Title: Benet 17.5 mg Tablets special drug use surveillance in patients with osseous Paget's disease (all-case surveillance) – 48-week surveillance –

NCT Number: NCT02106455

Statistical analysis plan Approve Date: 30-Mar-2018

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

Version 4.1: prepared on March 30, 2018

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 4.1

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to patient composition diagram • 5.(5)10) addition to imaging findings
Ver. 2.5	March 20, 2015	• 5.(5)2) addition to changes in excess serum ALP (subgroup analysis)
Ver. 2.6	March 25, 2016	• 4.(1) change in Data Lock Point
Ver. 2.7	June 2, 2016	• 5.(1) correction of patient composition diagram. • 5.(4)3) correction of a creation method for a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) correction of title of onset of adverse drug reactions by factors, number of digit of p-value, output method for “unknown (no entry)”, and errors • 5.(4)5) correction of title and creation method of onset of adverse drug reactions <stratified analysis>

Version No.	Date of preparation/revision	Site/reason for change
		• 5.(4)6) correction of title and creation method for a list of seriousness, date of onset, outcome of adverse drug reactions by factors
Ver. 3.0	May 17, 2017	• consistency of terminology “group” → “patients” • 2.(2) modification of description of patients included in safety evaluation • 2.(3) modification of description of patients included in efficacy evaluation • 5.(1) modification of description of patient composition diagram • 5.(2) modification of detailed description of patients excluded from safety evaluation and patients excluded from efficacy evaluation • 5.(3) modification of detailed description of discontinued/dropout patients, and addition of specification of “unknown” “no entry” • 5.(4)1) modification of list of onset of adverse drug reactions/infections (Separate form 2 of the notification of director of MHLW) and addition of number of the same patients, occurrences of same adverse drug reactions/infections • 5.(4)2) modification of description in the list of onset of serious adverse events (Separate form 2-2 of the notification of director of MHLW) and addition of number of the same patients, occurrences of same adverse drug reactions/infections • 5.(4)4) modification of description of onset of adverse drug reactions by factors • 5.(4)7) modification of description of comparison of adverse drug reaction profile after initial administration and re-administration 1 in individual patients • 5.(5) correction of “difference before and after administration” to “percent change” in efficacy analysis • 5.(5)1) modification of description of changes in excess serum ALP • 5.(5)2) modification of description of changes in excess serum ALP (subgroup analysis) • 5.(5)3) modification of description of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) modification of description of changes in serum ALP • 5.(5)6) modification of description of changes in serum ALP (subgroup analysis 2) • 5.(5)7) modification of description of changes in bone metabolism markers
Ver. 4.0	February 7, 2018	• Addition of terminology • 1. addition of application for re-examination to the purpose of analysis • 2.(2) correction of patients included in safety evaluation • 3. correction of handling of patients

Version No.	Date of preparation/revision	Site/reason for change
		• 4. (1) addition of date of starting survey to Data Lock Point, additions to the 12th and 13th Data Lock Points • 5.(4)1) addition of patient demographics • 5.(4)2) modification of description of a list of onset of adverse drug reactions/infections (Separate form 2 of the notification of director of MHLW), addition of tabulation by patient unit • 5.(4)3) modification of description of a list of onset of serious adverse events (Separate form 10 of the notification of director of MHLW), addition of tabulation by patient unit • 5.(4)4) modification of description in the list of seriousness, date of onset, outcome of adverse drug reactions, addition of priority of category items • 5.(4)5) correction of onset of adverse drug reactions by factors • 5.(4)6) deletion of a list of seriousness, date of onset, outcome of adverse drug reactions by factors • 5.(4)7) correction of adverse drug reaction profile after initial administration and re-administration in individual patients • 5.(4)9) addition of treatment compliance • 5.(4)10) addition of profile table of serious adverse drug reactions • 5.(4)11) addition of profile table of adverse drug reactions not foreseeable from “Precautions”. • 5.(5)1) modification of description of changes in excess serum ALP • 5.(5)2) correction of changes in excess serum ALP (subgroup analysis) • 5.(5)3) correction of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) modification of description of changes in serum ALP, addition of tabulation of percentage • 5.(5)5) correction of changes in serum ALP (subgroup analysis) • 5.(5)6) correction of changes in serum ALP (subgroup analysis 2) • 5.(5)8) deletion of changes in bone metabolism markers (subgroup analysis) • 5.(5)8) addition of tabulation by sites to evaluation of pain associated with osseous Paget’s disease • 5.(5)9) addition of other abnormal findings to imaging findings • 5.(7) addition of a list of summary of surveyed patients (Attachment form 3) • 5.(8)7) addition of handling of efficacy data to handling of patients receiving re-administration • 5.(8)9) addition of “tests” • 5.(8)10) addition of output of category “unknown”
Ver. 4.1	March 30, 2018	• 5.(4)2) correction of a list of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of the MHLW)

Version No.	Date of preparation/revision	Site/reason for change
		• 5.(4)9) correction of treatment compliance • 5.(5)1) correction of changes in excess serum ALP • 5.(5)2) correction of changes in excess serum ALP (subgroup analysis) • 5.(5)4) correction of changes in serum ALP • 5.(5)5) correction of changes in serum ALP (subgroup analysis)

Table of Contents

Terminology

Term	Explanation
Adverse event	All events recorded in [Adverse events] section of CRF. All untoward medical events encountered in a patient administered a medication (including abnormal laboratory data and infections). A causal relationship with this drug is not always clear.
Adverse drug reaction	Adverse events with “causal relationship with this drug” in [Adverse events] section of case report form (CRF) other than “not related”. However, an adverse event judged by the investigator as “not related” but judged by the sponsor as “related” is handled as an adverse drug reaction.
Serious adverse event	Adverse event for which “seriousness” in [Adverse events] section of CRF is “serious”. However, an adverse event judged by the investigator as “non-serious” but judged by the sponsor as “serious” is handled as a serious adverse drug reaction. Also, adverse events listed in the implementation guide as an “adverse event to be always judged serious” and “Takeda Medically Significant AE List” are included as well.

1. Purpose of analysis

To determine tabulation and analysis that are conducted for preparation of the documents for application for reexamination and a periodic safety report in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in safety evaluation" and "patients included in efficacy evaluation".

(2) Patients included in safety evaluation

Of the patients from whom a case report form (CRF) is collected, those who satisfy either of the following conditions are excluded from safety evaluation and others are included in safety evaluation.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) Of the patients with duplicated enrollment, those who were enrolled later.

iv) A patient for whom administration was started outside the enrollment period*

* The date of starting administration falls after the enrollment period of January 31, 2016 (on and after February 1, 2016).

(3) Patients included in efficacy evaluation

Of the patients included in safety evaluation, those who satisfy the following conditions are excluded from efficacy evaluation and others are included in efficacy evaluation.

i) patients from whom the information on efficacy before and after administration was not obtained.

3. Handling of patients

Unless otherwise specified, a patient recorded in a different CRF as a re-administered patient will be tabulated as one patient based on each CRF even if he/she is the same person. When tabulating the same patient as one patient, it should be clarified in "creation method" that tabulation is conducted for "each patient unit".

4. Data Lock Point

(1) Data Lock Point

Date of starting survey: August 1, 2008

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018, re-examination

13th: July 15, 2018, re-examination "(4) Safety analysis 10) Profile Table of serious adverse drug reactions, 11) Profile Table of adverse drug reactions not foreseeable from 'Precautions'"

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

<Analysis population>

Enrolled patients.

<Preparation method>

1) number of study sites
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) patients from whom CRF was not obtained, patients excluded from safety evaluation, and patients excluded from efficacy evaluation

Tabulate the number of patients in 1) to 6) above. Tabulate the number of patients according to reasons for 6). Of the patients from whom CRF was not obtained, output details in case other reason is applicable to a patient. Example) personal reason of a patient

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

<Analysis population>

Patients excluded from safety evaluation and patients excluded from efficacy evaluation.

<Preparation method>

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

<Analysis population>

Of the patients from whom CRF was collected, those who discontinued/dropped out.

<Preparation method>

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number. In case a reason for discontinuation/dropout is not known or specified, output as "unknown" and "no entry", respectively.

(4) Safety analysis

1) Patient demographics

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Calculate the number of patients and percentage for each item of patient demographics in Table (1). Calculate summary statistics for items with *. Conduct tabulation by patient unit. In case of tabulation by patient unit, use the information of patient demographics of initial administration.Table (1) Items of patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age (years)*	1) <65, 2) ≥65, 3) unknown
Height (cm)*	-
Weight (kg)*	-
Dosing category[*1]	1) initial administration, 2) re-administration
Dosing period (days)	1) ≤56 days, 2) ≥57 days, 3) unknown
Treatment category	1) outpatient, 2) inpatient, 3) outpatient ⇔ inpatient, 4) unknown
Diagnosis name (Osseous Paget's Disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Affected site[*2]	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*3]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*2*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*2*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other

Item	Category
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*2]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*2]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease[*5]	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*2*5*6]	1) calcitonin preparation, 2) etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug and etidronate, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*2*6]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: not necessary for tabulation by patient unit.

*2: tabulate presence or absence for each category (duplicate tabulation)

*3: morbid period starts on the "day of initial diagnosis of osseous Paget's disease" and ends on the "day of starting administration of this drug".

*4: classify disease names according to the MedDRA code

*5: include prior therapies in tabulation concerning the prior drugs for treatment of osseous Paget's disease.

*6: classify according to the JAPIC Code (drug data file)

2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notification No. 1027004 of Director of Pharmaceutical Evaluation Division dated October 27,2005. Attach a list of adverse drug reactions/infections by patient unit to the far right of this table.

Prepare a list of onset of adverse drug reactions according to administration category (initial administration, re-administration 1, re-administration 2, re-administration 3 onward) and treatment period (≤56 days, ≥57 days, unknown) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning

cumulative total section for the number of surveyed sites.

- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Number of occurrences of same adverse drug reactions/infections encountered in the same patient in (Note) 3

- In tabulation of SOC, several occurrences of the same SOC in a given patient is counted once.
- In tabulation of PT, several occurrences of the same PT in a given patient is counted once.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

3) List of occurrences of serious adverse events (Attachment form 10 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notification No. 1027004 of Director of Pharmaceutical Evaluation Division dated October 27,2005. Present serious adverse events by patient unit at the far right of this table.Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Number of adverse events encountered in the same patient in (Note) 4

- In tabulation of SOC, several occurrences of the same SOC in a given patient is counted once.
- In tabulation of PT, several occurrences of the same PT in a given patient is counted once.

4) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (2). Adverse drug reactions will be handled according to the "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Seriousness: serious>non-serious

Time of onset: event with earlier onset

Outcome: death> recovered with sequela> not recovered> improved> recovered >unknown

Prepare a list of adverse drug reactions according to administration category (initial administration, re-administration 1, re-administration 2, re-administration 3 onward) and treatment period (≤56 days, ≥57 days) in the same manner

Table (2) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown
Timing of onset[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 – 210, 9) Day 211 - 360, 10) Day 361 onward, 11) unknown
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

5) Onset of adverse drug reactions by factors

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Number of target patients, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (3). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

Table (3) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Age (years)	1) <65 years, 2) ≥65 years, 3) unknown
Weight (kg)[*1]	1) <[median], 2) ≥[median], 3) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (day)	1) ≤56 days, 2) ≥57 days, 3) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown

Item	Category
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
History of drug therapy for osseous Paget's disease[*5]	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3*5*6]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug and etidronate, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*3*6]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: determine the calculated value for [median]

*2: morbid period starts on the "day of initial diagnosis of osseous Paget's disease" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify disease names according to the MedDRA code

*5: tabulate prior therapies of osseous Paget's disease in the prior medication.

*6: classify according to the JAPIC Code (drug data file)

6) Onset of adverse drug reactions <stratified analysis>

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

The factors in "5) Onset of adverse drug reactions by factors" that show a significant difference ($p<0.05$) concerning presence or absence of adverse drug reactions will be stratified according to the above Table (3), and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA).

7) Profile of adverse drug reactions after initial administration and re-administration in individual patient

<Analysis population>

Patients included in safety evaluation who receive re-administration irrespective of onset of adverse drug reactions.

<Preparation method>

Presence or absence of adverse drug reactions after the initial administration and re-administration, adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome

will be recorded for each patient. Patients with “presence” of adverse drug reactions will be shown first, followed by patients with “absence” of adverse drug reactions in the order of case number at the initial administration.

8) Summary of interval of re-administration

<Analysis population>

Patients included in safety evaluation who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section “(8) Other arrangements”.

9) Treatment compliance

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Number of patients and percentage will be shown for “drugs are taken as instructed (compliance of ≥90%)”, “sometimes forget taking drugs (compliance of ≥67% and <90%)”, “taking drugs half the time (compliance of ≥25% and <67%)”, “hardly taking the drug (compliance of <25%)”, and “unknown”.

10) Profile table of serious adverse drug reactions

<Analysis population>

All patients in spontaneous reporting, literature, drug use surveillance, special drug use survey, clinical trials, post-marketing clinical trials, and a clinical trial conducted by other pharmaceutical company.

<Preparation method>

Concerning serious adverse drug reactions, number of patients will be calculated for each type of adverse drug reactions (according to SOC and PT) by the timing of onset and outcome category shown in Table (2). In case of several occurrences of the same adverse event/adverse drug reaction (LLT) in a given patient, they will be tabulated as one according to the priority order in 4). Events with the same PT but different LLT will be tabulated as separate events.

11) Profile table of adverse drug reactions not foreseeable from “Precautions”

<Analysis population>

All patients in spontaneous reporting, literature, drug use surveillance, special drug use survey, clinical trials, post-marketing clinical trials, and a clinical trial conducted by other pharmaceutical company.

<Preparation method>

Concerning the adverse drug reactions not foreseeable from “Precautions”, number of patients for each types of adverse drug reactions (SOC, PT) will be calculated based on the categories of seriousness, timing of onset, and outcome shown in Table (2). In case of several occurrences of the same adverse event/adverse drug reaction (LLT) in a given patient, they will be tabulated as one according to the priority order in 4). Events with the same PT but different LLT will be tabulated as separate events.

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in efficacy evaluation. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics and two-sided 95% confidence interval will be shown. A paired t-test will be conducted for percent change and p-value of test results will be shown. Details of handling of data at each time point will be shown in “(8) Other arrangements 5) Data of evaluation time point”.

A graph showing changes in mean ± standard deviation will be prepared for the measured values at each time point and percent change.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without re-administration and the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics and two-sided 95% confidence interval will be shown. A paired t-test will be conducted for percent change and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

i) Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

ii) Patients who received initial administration. However, it is not applicable to administration categories 1 and 2 because they are comparison with the initial administration.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (4) to calculate the measured values at each time point and percent change from baseline. Summary statistics and two-sided 95% confidence interval will be conducted. Paired t-test will be conducted for percent change and p-value will be shown for the test result.

Table (4) Stratified categories

Item	Category
Sex	1) M, 2) F
Age	1) <65 years, 2) ≥65 years
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic
Administration category 1	1) initial, 2) re-administration
Administration category 2	1) initial, 2) re-administration 1, 3) re-administration 2 onward
Prior medication for osseous Paget's disease[*1*2]	1) No, 2) Yes
Prior administration of bisphosphonate product[*1*2]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease[*2]	1) No, 2) Yes
Renal disease	1) No, 2) Yes
Hepatic disease	1) No, 2) Yes

*1: prior medication (administration within 8 weeks of baseline)

*2: classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in efficacy evaluation who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration, re-administration 1 and re-administration 2 will be shown for each patient.

4) Changes in serum ALP

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics and two-sided 95% confidence interval will be shown. Paired t-test will be conducted for percent change and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

A graph showing changes in mean ± standard deviation will be prepared for the measured value at each time point and percent change.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial administration alone without re-administration and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics and two-sided 95% confidence interval will be shown. Paired t-test will be conducted for percent change and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

Of the patients whose upper limit of the site reference value* is available among those who receive initial administration, percentage of patients will be calculated in whom post-dose serum ALP is lowered by 10% compared with baseline and <2-fold of the upper limit of the site reference value at each time point.

* In case baseline site reference value is available but post-dose site reference value is missing, complement data with baseline site reference value.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

i) Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

ii) Patients who received initial administration. However, it is not applicable to administration categories 1 and 2 because they are comparison with the initial administration.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (4), measured value at each time point and percent change from baseline will be calculated and summary statistics and two-sided 95% confidence interval will be shown. Paired t-test will be conducted for percent change and p-value will be shown for the test result.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in efficacy evaluation and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration, re-administration 1 and 2 will be shown for each patient.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for percent change, and p-value will be shown for the test result. A graph showing changes over time in mean ± standard deviation will be prepared for the measured values. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

8) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

Number of patients with pain associated with osseous Paget's disease by the site of pain and percentage will be calculated at each time point.

9) Imaging findings

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology, trabecular bone structure, and other abnormal findings by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved

Baseline	Post-dose	Evaluation
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "2) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "4) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) List of summary of surveyed patients (Attachment form 3)

<Analysis population>

Patients from whom CRF is collected.

<Preparation method>

A list will be prepared to show case No., site name, founding organization/code, prefecture, patient initials, sex, age, inpatient/outpatient, reason for use (disease code, disease name), severity at baseline, complication (presence or absence, number listed, name), route of administration, maximum dose (day/dosage), mean dose (day/dosage), unit, number of daily administration (maximum), administration period, concomitant drug (drug code, typical name of drug, numbers listed), extent of efficacy, adverse drug reactions (organ code, adverse drug reaction code, adverse drug reaction name, presence or absence, number listed), outcome, CRF No. and dropout according to the CRF number.

(8) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (5) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (5) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference

value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

A previous case will be completed when re-administration is started. Accordingly, the efficacy data after the start of re-administration recorded in the prior CRF will not be used.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

9) Tests

Tests will be conducted by excluding “unknown”. p-value will be calculated up to the 4^{th} decimal place (round up to the 4^{th} decimal place).

10) Output of category “unknown”

In case category is “unknown” and target number of patients is 0, category “unknown” is not outputted.

Version 4.0: prepared on February, 7, 2018

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 4.0

Takeda Pharmaceutical Co., Ltd.

PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to patient composition diagram • 5.(5)10) addition to imaging findings
Ver. 2.5	March 20, 2015	• 5.(5)2) addition to changes in excess serum ALP (subgroup analysis)
Ver. 2.6	March 25, 2016	• 4.(1) change in Data Lock Point
Ver. 2.7	June 2, 2016	• 5.(1) correction of patient composition diagram. • 5.(4)3) correction of a creation method for a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) correction of title of onset of adverse drug reactions by factors, number of digit of p-value, output method for “unknown (no entry)”, and errors • 5.(4)5) correction of title and creation method of onset of adverse drug reactions <stratified analysis>

Version No.	Date of preparation/revision	Site/reason for change
		• 5.(4)6) correction of title and creation method for a list of seriousness, date of onset, outcome of adverse drug reactions by factors
Ver. 3.0	May 17, 2017	• consistency of terminology “group” → “patients” • 2.(2) modification of description of patients included in safety evaluation • 2.(3) modification of description of patients included in efficacy evaluation • 5.(1) modification of description of patient composition diagram • 5.(2) modification of detailed description of patients excluded from safety evaluation and patients excluded from efficacy evaluation • 5.(3) modification of detailed description of discontinued/dropout patients, and addition of specification of “unknown” “no entry” • 5.(4)1) modification of list of onset of adverse drug reactions/infections (Separate form 2 of the notification of director of MHLW) and addition of number of the same patients, occurrences of same adverse drug reactions/infections • 5.(4)2) modification of description in the list of onset of serious adverse events (Separate form 2-2 of the notification of director of MHLW) and addition of number of the same patients, occurrences of same adverse drug reactions/infections • 5.(4)4) modification of description of onset of adverse drug reactions by factors • 5.(4)7) modification of description of comparison of adverse drug reaction profile after initial administration and re-administration 1 in individual patients • 5.(5) correction of “difference before and after administration” to “percent change” in efficacy analysis • 5.(5)1) modification of description of changes in excess serum ALP • 5.(5)2) modification of description of changes in excess serum ALP (subgroup analysis) • 5.(5)3) modification of description of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) modification of description of changes in serum ALP • 5.(5)6) modification of description of changes in serum ALP (subgroup analysis 2) • 5.(5)7) modification of description of changes in bone metabolism markers
Ver. 4.0	February 7, 2018	• Addition of terminology • 1. addition of application for re-examination to the purpose of analysis • 2.(2) correction of patients included in safety evaluation • 3. correction of handling of patients

Version No.	Date of preparation/revision	Site/reason for change
		• 4. (1) addition of date of starting survey to Data Lock Point, additions to the 12th and 13th Data Lock Points • 5.(4)1) addition of patient demographics • 5.(4)2) modification of description of a list of onset of adverse drug reactions/infections (Separate form 2 of the notification of director of MHLW), addition of tabulation by patient unit • 5.(4)3) modification of description of a list of onset of serious adverse events (Separate form 10 of the notification of director of MHLW), addition of tabulation by patient unit • 5.(4)4) modification of description in the list of seriousness, date of onset, outcome of adverse drug reactions, addition of priority of category items • 5.(4)5) correction of onset of adverse drug reactions by factors • 5.(4)6) deletion of a list of seriousness, date of onset, outcome of adverse drug reactions by factors • 5.(4)7) correction of adverse drug reaction profile after initial administration and re-administration in individual patients • 5.(4)9) addition of treatment compliance • 5.(4)10) addition of profile table of serious adverse drug reactions • 5.(4)11) addition of profile table of adverse drug reactions not foreseeable from “Precautions”. • 5.(5)1) modification of description of changes in excess serum ALP • 5.(5)2) correction of changes in excess serum ALP (subgroup analysis) • 5.(5)3) correction of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) modification of description of changes in serum ALP, addition of tabulation of percentage • 5.(5)5) correction of changes in serum ALP (subgroup analysis) • 5.(5)6) correction of changes in serum ALP (subgroup analysis 2) • 5.(5)8) deletion of changes in bone metabolism markers (subgroup analysis) • 5.(5)8) addition of tabulation by sites to evaluation of pain associated with osseous Paget’s disease • 5.(5)9) addition of other abnormal findings to imaging findings • 5.(7) addition of a list of summary of surveyed patients (Attachment form 3) • 5.(8)7) addition of handling of efficacy data to handling of patients receiving re-administration • 5.(8)9) addition of “tests” • 5.(8)10) addition of output of category “unknown”

Table of Contents

Terminology

Term	Explanation
Adverse event	All events recorded in [Adverse events] section of CRF. All untoward medical events encountered in a patient administered a medication (including abnormal laboratory data and infections). A causal relationship with this drug is not always clear.
Adverse drug reaction	Adverse events with “causal relationship with this drug” in [Adverse events] section of case report form (CRF) other than “not related”. However, an adverse event judged by the investigator as “not related” but judged by the sponsor as “related” is handled as an adverse drug reaction.
Serious adverse event	Adverse event for which “seriousness” in [Adverse events] section of CRF is “serious”. However, an adverse event judged by the investigator as “non-serious” but judged by the sponsor as “serious” is handled as a serious adverse drug reaction. Also, adverse events listed in the implementation guide as an “adverse event to be always judged serious” and “Takeda Medically Significant AE List” are included as well.

1. Purpose of analysis

To determine tabulation and analysis that are conducted for preparation of the documents for application for reexamination and a periodic safety report in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in safety evaluation" and "patients included in efficacy evaluation".

(2) Patients included in safety evaluation

Of the patients from whom a case report form (CRF) is collected, those who satisfy either of the following conditions are excluded from safety evaluation and others are included in safety evaluation.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) Of the patients with duplicated enrollment, those who were enrolled later.

iv) A patient for whom administration was started outside the enrollment period*

* The date of starting administration falls after the enrollment period of January 31, 2016 (on and after February 1, 2016).

(3) Patients included in efficacy evaluation

Of the patients included in safety evaluation, those who satisfy the following conditions are excluded from efficacy evaluation and others are included in efficacy evaluation.

i) patients from whom the information on efficacy before and after administration was not obtained.

3. Handling of patients

Unless otherwise specified, a patient recorded in a different CRF as a re-administered patient will be tabulated as one patient based on each CRF even if he/she is the same person. When tabulating the same patient as one patient, it should be clarified in "creation method" that tabulation is conducted for "each patient unit".

4. Data Lock Point

(1) Data Lock Point

Date of starting survey: August 1, 2008

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018, re-examination

13th: July 15, 2018, re-examination "(4) Safety analysis 10) Profile Table of serious adverse drug reactions, 11) Profile Table of adverse drug reactions not foreseeable from 'Precautions'"

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

<Analysis population>

Enrolled patients.

<Preparation method>

1) number of study sites
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) patients from whom CRF was not obtained, patients excluded from safety evaluation, and patients excluded from efficacy evaluation

Tabulate the number of patients in 1) to 6) above. Tabulate the number of patients according to reasons for 6). Of the patients from whom CRF was not obtained, output details in case other reason is applicable to a patient. Example) personal reason of a patient

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

<Analysis population>

Patients excluded from safety evaluation and patients excluded from efficacy evaluation.

<Preparation method>

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

<Analysis population>

Of the patients from whom CRF was collected, those who discontinued/dropped out.

<Preparation method>

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number. In case a reason for discontinuation/dropout is not known or specified, output as "unknown" and "no entry", respectively.

(4) Safety analysis

1) Patient demographics

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Calculate the number of patients and percentage for each item of patient demographics in Table (1). Calculate summary statistics for items with *. Conduct tabulation by patient unit. In case of tabulation by patient unit, use the information of patient demographics of initial administration.Table (1) Items of patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age (years)*	1) <65, 2) ≥65, 3) unknown
Height (cm)*	-
Weight (kg)*	-
Dosing category[*1]	1) initial administration, 2) re-administration
Dosing period (days)	1) ≤56 days, 2) ≥57 days, 3) unknown
Treatment category	1) outpatient, 2) inpatient, 3) outpatient ⇔ inpatient, 4) unknown
Diagnosis name (Osseous Paget's Disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Affected site[*2]	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*3]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*2*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*2*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other

Item	Category
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*2]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*2]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease[*5]	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*2*5*6]	1) calcitonin preparation, 2) etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug and etidronate, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*2*6]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: not necessary for tabulation by patient unit.

*2: tabulate presence or absence for each category (duplicate tabulation)

*3: morbid period starts on the "day of initial diagnosis of osseous Paget's disease" and ends on the "day of starting administration of this drug".

*4: classify disease names according to the MedDRA code

*5: include prior therapies in tabulation concerning the prior drugs for treatment of osseous Paget's disease.

*6: classify according to the JAPIC Code (drug data file)

2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notification No. 1027004 of Director of Pharmaceutical Evaluation Division dated October 27,2005. Attach a list of adverse drug reactions/infections by patient unit to the far right of this table.

Prepare a list of onset of adverse drug reactions according to administration category (initial administration, re-administration 1, re-administration 2, re-administration 3 onward) and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning

cumulative total section for the number of surveyed sites.

- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Number of occurrences of same adverse drug reactions/infections encountered in the same patient in (Note) 3

- In tabulation of SOC, several occurrences of the same SOC in a given patient is counted once.
- In tabulation of PT, several occurrences of the same PT in a given patient is counted once.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

3) List of occurrences of serious adverse events (Attachment form 10 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notification No. 1027004 of Director of Pharmaceutical Evaluation Division dated October 27,2005. Present serious adverse events by patient unit at the far right of this table.Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Number of adverse events encountered in the same patient in (Note) 4

- In tabulation of SOC, several occurrences of the same SOC in a given patient is counted once.
- In tabulation of PT, several occurrences of the same PT in a given patient is counted once.

4) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (2). Adverse drug reactions will be handled according to the "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Seriousness: serious>non-serious

Time of onset: event with earlier onset

Outcome: death> recovered with sequela> not recovered> improved> recovered >unknown

Prepare a list of adverse drug reactions according to administration category (initial administration, re-administration 1, re-administration 2, re-administration 3 onward) and treatment period (≤56 days, ≥57 days) in the same manner.

Table (2) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown
Timing of onset[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 – 210, 9) Day 211 - 360, 10) Day 361 onward, 11) unknown
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

5) Onset of adverse drug reactions by factors

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Number of target patients, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (3). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

Table (3) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Age (years)	1) <65 years, 2) ≥65 years, 3) unknown
Weight (kg)[*1]	1) <[median], 2) ≥[median], 3) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (day)	1) ≤56 days, 2) ≥57 days, 3) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown

Item	Category
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
History of drug therapy for osseous Paget's disease[*5]	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3*5*6]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug and etidronate, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*3*6]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: determine the calculated value for [median]

*2: morbid period starts on the "day of initial diagnosis of osseous Paget's disease" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify disease names according to the MedDRA code

*5: tabulate prior therapies of osseous Paget's disease in the prior medication.

*6: classify according to the JAPIC Code (drug data file)

6) Onset of adverse drug reactions <stratified analysis>

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

The factors in "5) Onset of adverse drug reactions by factors" that show a significant difference ($p<0.05$) concerning presence or absence of adverse drug reactions will be stratified according to the above Table (3), and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA).

7) Profile of adverse drug reactions after initial administration and re-administration in individual patient

<Analysis population>

Patients included in safety evaluation who receive re-administration irrespective of onset of adverse drug reactions.

<Preparation method>

Presence or absence of adverse drug reactions after the initial administration and re-administration, adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome

will be recorded for each patient. Patients with “presence” of adverse drug reactions will be shown first, followed by patients with “absence” of adverse drug reactions in the order of case number at the initial administration.

8) Summary of interval of re-administration

<Analysis population>

Patients included in safety evaluation who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section “(8) Other arrangements”.

9) Treatment compliance

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Number of patients and percentage will be shown for “drugs are taken as instructed (compliance of ≥90%)”, “sometimes forget taking drugs (compliance of ≥67% and <90%)”, “taking drugs half the time (compliance of ≥25% and <67%)”, and “hardly taking the drug (compliance of <25%).”

10) Profile table of serious adverse drug reactions

<Analysis population>

All patients in spontaneous reporting, literature, drug use surveillance, special drug use survey, clinical trials, post-marketing clinical trials, and a clinical trial conducted by other pharmaceutical company.

<Preparation method>

Concerning serious adverse drug reactions, number of patients will be calculated for each type of adverse drug reactions (according to SOC and PT) by the timing of onset and outcome category shown in Table (2). In case of several occurrences of the same adverse event/adverse drug reaction (LLT) in a given patient, they will be tabulated as one according to the priority order in 4). Events with the same PT but different LLT will be tabulated as separate events.

11) Profile table of adverse drug reactions not foreseeable from “Precautions”

<Analysis population>

All patients in spontaneous reporting, literature, drug use surveillance, special drug use survey, clinical trials, post-marketing clinical trials, and a clinical trial conducted by other pharmaceutical company.

<Preparation method>

Concerning the adverse drug reactions not foreseeable from "Precautions", number of patients for each types of adverse drug reactions (SOC, PT) will be calculated based on the categories of seriousness, timing of onset, and outcome shown in Table (2). In case of several occurrences of the same adverse event/adverse drug reaction (LLT) in a given patient, they will be tabulated as one according to the priority order in 4). Events with the same PT but different LLT will be tabulated as separate events.

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in efficacy evaluation. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for percent change and p-value of test results will be shown. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

A graph showing changes in mean ± standard deviation will be prepared for the measured values at each time point and percent change.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without re-administration and the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for percent change and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

i) Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

ii) Patients who received initial administration. However, it is not applicable to administration categories 1 and 2 because they are comparison with the initial administration.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (4) Stratified categories

Item	Category
Sex	1) M, 2) F
Age	1) <65 years, 2) ≥65 years
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic
Administration category 1	1) initial, 2) re-administration
Administration category 2	1) initial, 2) re-administration 1, 3) re-administration 2 onward
Prior medication for osseous Paget's disease[*1*2]	1) No, 2) Yes
Prior administration of bisphosphonate product[*1*2]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease[*2]	1) No, 2) Yes
Renal disease	1) No, 2) Yes
Hepatic disease	1) No, 2) Yes

*1: prior medication (administration within 8 weeks of baseline)

*2: classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in efficacy evaluation who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration, re-administration 1 and re-administration 2 will be shown for each patient.

4) Changes in serum ALP

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for percent change and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

A graph showing changes in mean ± standard deviation will be prepared for the measured value at each time point and percent change.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial

administration alone without re-administration and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for percent change and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

Of the patients whose upper limit of the site reference value* is available among those who receive initial administration, percentage of patients will be calculated in whom post-dose serum ALP is lowered by 10% compared with baseline and <2-fold of the upper limit of the site reference value at each time point.

* In case baseline site reference value is available but post-dose site reference value is missing, complement data with baseline site reference value.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

i) Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

ii) Patients who received initial administration. However, it is not applicable to administration categories 1 and 2 because they are comparison with the initial administration.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in efficacy evaluation and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration, re-administration 1 and 2 will be shown for each patient.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone

metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for percent change, and p-value will be shown for the test result. A graph showing changes over time in mean ± standard deviation will be prepared for the measured values. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

8) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

Number of patients with pain associated with osseous Paget's disease by the site of pain and percentage will be calculated at each time point.

9) Imaging findings

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology, trabecular bone structure, and other abnormal findings by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(8) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "2) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "4) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) List of summary of surveyed patients (Attachment form 3)

<Analysis population>

Patients from whom CRF is collected.

<Preparation method>

A list will be prepared to show case No., site name, founding organization/code, prefecture, patient initials, sex, age, inpatient/outpatient, reason for use (disease code, disease name), severity at baseline, complication (presence or absence, number listed, name), route of administration, maximum dose (day/dosage), mean dose (day/dosage), unit, number of daily administration (maximum), administration period, concomitant drug (drug code, typical name of drug, numbers listed), extent of efficacy, adverse drug reactions (organ code, adverse drug reaction code, adverse drug reaction name, presence or absence, number listed), outcome, CRF No. and dropout according to the CRF number.

(8) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (5) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (5) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become "0" when calculating percent change 4). When excess serum ALP becomes "0", calculate the value as "0.01".

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

A previous case will be completed when re-administration is started. Accordingly, the efficacy data after the start of re-administration recorded in the prior CRF will not be used.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

9) Tests

Tests will be conducted by excluding “unknown”. p-value will be calculated up to the 4^{th} decimal place (round up to the 4^{th} decimal place).

10) Output of category “unknown”

In case category is “unknown” and target number of patients is 0, category “unknown” is not outputted.

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 3.0

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to patient composition diagram • 5.(5)10) addition to imaging findings
Ver. 2.5	March 20, 2015	• 5.(5)2) addition to changes in excess serum ALP (subgroup analysis)
Ver. 2.6	March 25, 2016	• 4.(1) change in Data Lock Point
Ver. 2.7	June 2, 2016	• 5.(1) correction of patient composition diagram. • 5.(4)3) correction of a creation method for a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) correction of title of onset of adverse drug reactions by factors, number of digit of p-value, output method for “unknown (no entry)”, and errors • 5.(4)5) correction of title and creation method of onset of adverse drug

Version No.	Date of preparation/revision	Site/reason for change
		reactions <stratified analysis> • 5.(4)6) correction of title and creation method for a list of seriousness, date of onset, outcome of adverse drug reactions by factors
Ver. 3.0	May 17, 2017	• consistency of terminology “group” → “patients” • 2.(2) modification of description of patients included in safety evaluation • 2.(3) modification of description of patients included in efficacy evaluation • 5.(1) modification of description of patient composition diagram • 5.(2) modification of detailed description of patients excluded from safety evaluation and patients excluded from efficacy evaluation • 5.(3) modification of detailed description of discontinued/dropout patients, and addition of specification of “unknown” “no entry” • 5.(4)1) modification of list of onset of adverse drug reactions/infections (Separate form 2 of the notification of director of MHLW) and addition of number of the same patients, occurrences of same adverse drug reactions/infections • 5.(4)2) modification of description in the list of onset of serious adverse events (Separate form 2-2 of the notification of director of MHLW) and addition of number of the same patients, occurrences of same adverse drug reactions/infections • 5.(4)4) modification of description of onset of adverse drug reactions by factors • 5.(4)7) modification of description of comparison of adverse drug reaction profile after initial administration and re-administration 1 in individual patients • 5.(5) correction of “difference before and after administration” to “percent change” in efficacy analysis • 5.(5)1) modification of description of changes in excess serum ALP • 5.(5)2) modification of description of changes in excess serum ALP (subgroup analysis) • 5.(5)3) modification of description of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) modification of description of changes in serum ALP • 5.(5)6) modification of description of changes in serum ALP (subgroup analysis 2) • 5.(5)7) modification of description of changes in bone metabolism markers

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in safety evaluation" and "patients included in efficacy evaluation".

(2) Patients included in safety evaluation

Of the patients from whom a case report form (CRF) is collected, those who satisfy either of the following conditions are excluded from safety evaluation and others are included in safety evaluation.

i) A patient under follow-up (not fixed because not approved at the patient level)

ii) A patient not administered this drug

iii) A patient in whom onset of adverse event is unknown

iv) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in efficacy evaluation

Of the patients included in safety evaluation, those who satisfy the following conditions are excluded from efficacy evaluation and others are included in efficacy evaluation.

i) patients from whom the information on efficacy before and after administration was not obtained.

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

<Analysis population>

Enrolled patients.

<Preparation method>

1) number of study sites
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) patients from whom CRF was not obtained, patients excluded from safety evaluation, and patients excluded from efficacy evaluation

Tabulate the number of patients in 1) to 6) above. Tabulate the number of patients according to reasons for 6). Of the patients from whom CRF was not obtained, output details in case other reason is applicable to a patient. Example) personal reason of a patient

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

<Analysis population>

Patients excluded from safety evaluation and patients excluded from efficacy evaluation.

<Preparation method>

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of

patient number.

(3) Details of discontinued/dropout patients

<Analysis population>

Of the patients from whom CRF was collected, those who discontinued/dropped out.

<Preparation method>

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number. In case a reason for discontinuation/dropout is not known or specified, output as “unknown” and “no entry”, respectively.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Prepare according to (Note) 1 to 8 in Attachment form 2 of PFSB/ELD Notifications Nos. 0517-4 and 0517-1 of Directors of Pharmaceutical Evaluation and Safety Divisions dated May 17, 2013.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Number of occurrences of same adverse drug reactions/infections encountered in the same patient in (Note) 3

- In tabulation of SOC, several occurrences of the same SOC in a given patient is counted once.
- In tabulation of PT, several occurrences of the same PT in a given patient is counted once.

Infections in (Note) 8

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 8

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Prepare according to (Notes) 1 to 9 in Attachment form 2-2 of PFSB/ELD Notifications Nos. 0517-4 and 0517-1 of Directors of Pharmaceutical Evaluation and Safety Divisions dated May 17, 2013. Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Number of adverse events encountered in the same patient in (Note) 4

- In tabulation of SOC, several occurrences of the same SOC in a given patient is counted once.
- In tabulation of PT, several occurrences of the same PT in a given patient is counted once.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 – 210, 9) Day 211 - 360, 10) Day 361 onward, 11) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown/not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by factors

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Number of target patients, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to four decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Data will not be printed out if its category is "unknown/not provided" and the number of patients for that category is 0.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient → inpatient, 3) inpatient, 4) inpatient → outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1/2 year, 2) ≥1/2 and <1 year, 3) ≥1 and <2 years, 4) ≥2 and <3 years, 5) ≥3 and <5 years, 6) ≥5 years, 7) unknown (not provided)
Complication	1) none, 2) present, 3) unknown

Item	Category
Details of complication*3*4	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history*3*4	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity*3	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease *3	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease*3	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs*3*4	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osseous Paget's disease" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) Onset of adverse drug reactions <stratified analysis>

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by factors," and each adverse drug reaction will be tabulated according to "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of

MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests. [Table 4.5]

6) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in safety evaluation.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed [Table 4.6].

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual patient

<Analysis population>

Patients included in safety evaluation who experienced adverse drug reactions after either initial administration or initial re-administration.

<Preparation method>

Presence or absence of adverse drug reactions after the initial administration and initial re-administration, adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Patients included in safety evaluation who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in efficacy evaluation. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for percent change and

p-value of test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point" (Table 5.1).

A graph showing changes in mean ± standard deviation will be prepared for the measured values at each time point and percent change.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for percent change and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (3) Stratified categories

Item	Category
Sex	1) M, 2) F
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in efficacy evaluation who receive re-administration. However, a patient without baseline or

post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be shown for each patient. In addition, individual graphs showing changes over time will be generated for the initial administration and re-administration 1.

4) Changes in serum ALP

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for percent change and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

A graph showing changes in mean ± standard deviation will be prepared for the measured value at each time point and percent change.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial administration alone and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for percent change and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in efficacy evaluation and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be shown for each patient. In addition, individual graphs showing changes over time will be generated for the initial administration and re-administration 1.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for percent change, and p-value will be shown for the test result. A graph showing changes over time in mean ± standard deviation will be prepared for the measured values. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (3), and analyses similar to those described in "7) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed. [Table 5.8]

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Patients included in efficacy evaluation. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (4) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (4) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

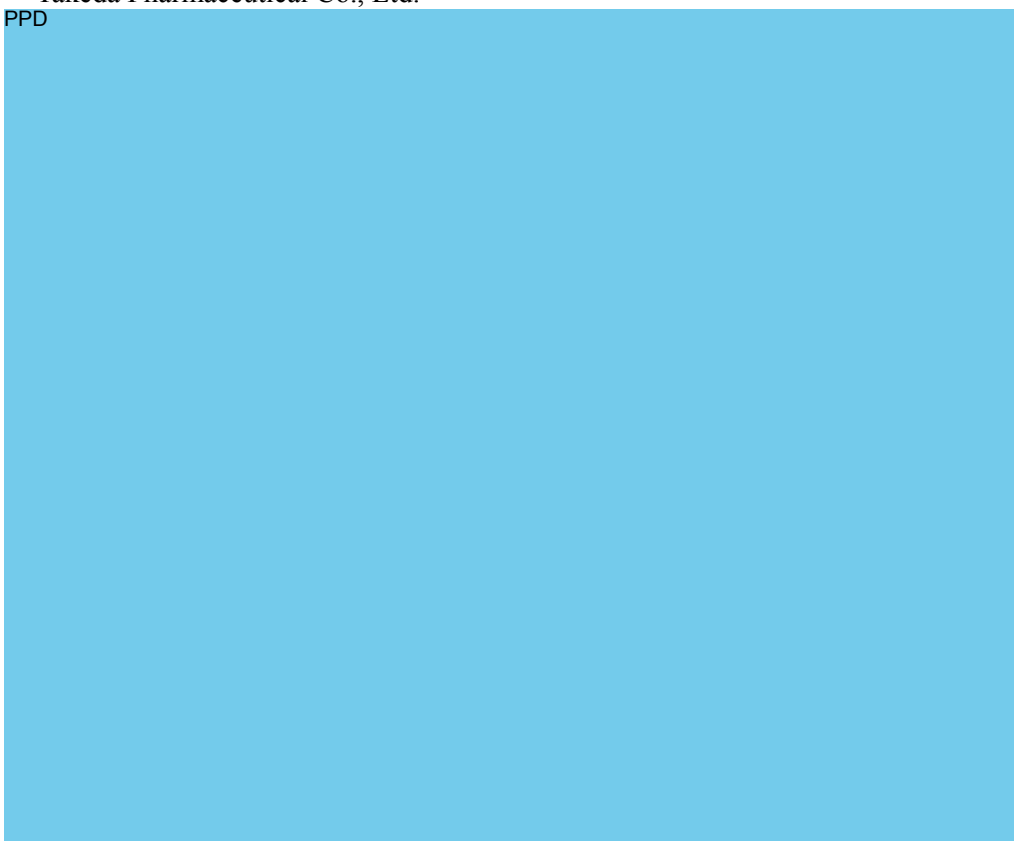
interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Version 2.7: prepared on June 2, 2016

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.7

Takeda Pharmaceutical Co., Ltd.
PPD



Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of subjects excluded from safety data analysis and subjects excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of subjects excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual subjects. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each subject, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each subject, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to subject composition diagram • 5.(5)10) addition to imaging findings
Ver. 2.5	March 20, 2015	• 5.(5)2) addition to changes in excess serum ALP (subgroup analysis)
Ver. 2.6	March 25, 2016	• 4.(1) change in Data Lock Point
Ver. 2.7	June 2, 2016	• 5.(1) correction of subject composition diagram. • 5.(4)3) correction of a creation method for a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) correction of title of onset of adverse drug reactions by factors, number of digit of p-value, output method for “unknown (no entry)”, and errors • 5.(4)5) correction of title and creation method of onset of adverse drug

Version No.	Date of preparation/revision	Site/reason for change
		reactions <stratified analysis> • 5.(4)6) correction of title and creation method for a list of seriousness, date of onset, outcome of adverse drug reactions by factors

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Subjects included in the safety evaluation set" and "subjects included in the efficacy evaluation set".

(2) Subjects included in the safety evaluation set

The subjects who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A subject not administered this drug

ii) A subject in whom onset of adverse event is unknown

iii) A subject found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Subjects included in the efficacy evaluation set

Of the subjects included in the safety evaluation set, those who do not meet the following conditions are included in the efficacy evaluation set.

i) subjects from whom the information on efficacy before and after administration was not obtained.

3. Handling of subjects and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Subject composition diagram

1) number of study sites
2) number of enrolled subjects
3) number of subjects from whom CRF was collected
4) number of subjects included in safety evaluation
5) number of subjects included in efficacy evaluation
6) Tabulate the number of "subjects from whom CRF was not obtained," "subjects excluded from safety evaluation," and "subjects excluded from efficacy evaluation" by reasonOf the subjects from whom CRF was not obtained, output details in case other reason is applicable to a subject. Example) personal reason of a patient

(2) Details of subjects excluded from safety evaluation and subjects excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of subject number.

(3) Details of discontinued/dropout subjects

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of subject number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Subjects included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Subjects included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 2-2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Subjects included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days, unknown) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 – 210, 9) Day 211 - 360, 10) Day 361 onward, 11) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown/not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by factors

<Analysis population>

Subjects included in the safety evaluation set.

<Preparation method>

Number of subjects surveyed, number of subjects with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety [Table 4.4].

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to four decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Data will not be printed out if its category is "unknown/not provided" and the number of subjects for that category is 0.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown

Item	Category
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown

Item	Category
Details of history of drug therapy for osseous Paget's disease[*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*3*4]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osseous Paget's disease" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) Onset of adverse drug reactions <stratified analysis>

<Analysis population>

Subjects included in the safety evaluation set.

<Preparation method>

Subjects will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests. [Table 4.5]

6) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Subjects included in the safety evaluation set.

<Preparation method>

Subjects will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual subject

<Analysis population>

Subjects included in the safety evaluation set who receive re-administration.

<Preparation method>

For patients experiencing adverse drug reactions after either initial administration or re-administration 1, the presence or absence of adverse drug reactions after the initial administration and initial re-administration, adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Subjects included in the safety evaluation set who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Subjects included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value of test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured values at each time point.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of subjects who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (3) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Subjects included in the efficacy evaluation set who receive re-administration. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

4) Changes in serum ALP

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured

value at each time point.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all subjects. A graph showing changes over time will be prepared for subjects who received initial administration alone and at initial administration in subjects who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each subject who receives re-administration.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Subjects included in the efficacy evaluation set and who receive re-administration. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

7) Changes in bone metabolism markers

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of

handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, subjects will be stratified according to the items listed in Table (3), and analyses similar to those described in "7) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Subjects included in the efficacy evaluation set. However, a subject without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved

Baseline	Post-dose	Evaluation
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of subjects excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Subjects excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Subjects excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (4) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (4) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become "0" when calculating percent change 4). When excess serum ALP becomes "0", calculate the value as "0.01".

7) Handling of subjects who receive re-administration

Initial administration and re-administration will be judged based on "administration category" of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Version 2.6: prepared on March 25, 2016

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.6

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to patient composition diagram • 5.(5)10) addition to imaging findings
Ver. 2.5	March 20, 2015	• 5.(5)2) addition to changes in excess serum ALP (subgroup analysis)
Ver. 2.6	March 25, 2016	• 4.(1) change in Data Lock Point

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) patients from whom the information on efficacy before and after administration was not obtained.

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reasonOf the patients from whom CRF was not obtained, output details in case other reason is applicable to a patient. Example) personal reason of a patient

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown/not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown

Item	Category
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown

Item	Category
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs*3*4	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual patient

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

For patients experiencing adverse drug reactions after either initial administration or re-administration 1, the presence or absence of adverse drug reactions after the initial administration and initial re-administration,

adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value of test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured values at each time point.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (3) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

4) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured value at each time point.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial administration alone and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients

who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in “(7) Other arrangements 5) Data of evaluation time point”.

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (3), and analyses similar to those described in "7) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (4) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of

(N+1) times will be used

Table (4) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.5

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to patient composition diagram • 5.(5)10) addition to imaging findings
Ver. 2.5	March 20, 2015	• 5.(5)2) addition to changes in excess serum ALP (subgroup analysis)

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) patients from whom the information on efficacy before and after administration was not obtained.

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: September 30, 2014

10th: September 30, 2015

11th: September 30, 2016

12th: September 30, 2017

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reasonOf the patients from whom CRF was not obtained, output details in case other reason is applicable to a patient. Example) personal reason of a patient

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown/not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown

Item	Category
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) *1	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category *1	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period*2	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication*3*4	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history*3*4	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity*3	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease *3	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease*3	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown

Item	Category
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs*3*4	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual patient

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

For patients experiencing adverse drug reactions after either initial administration or re-administration 1, the presence or absence of adverse drug reactions after the initial administration and initial re-administration,

adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value of test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured values at each time point.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (3) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

4) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured value at each time point.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from

baseline in all patients. A graph showing changes over time will be prepared for patients who received initial administration alone and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in “(7) Other arrangements 5) Data of evaluation time point”.

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (3), and analyses similar to those described in "7) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (4) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (4) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Version 2.4: prepared on July 5, 2013

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.4

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.
Ver. 2.4	July 5, 2013	• 2.(3) correction of efficacy analysis population • 4.(1) change in Data Lock Point • 5.(1) addition to patient composition diagram • 5.(5)10) addition to imaging findings

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) patients from whom the information on efficacy before and after administration was not obtained.

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: September 30, 2014

10th: September 30, 2015

11th: September 30, 2016

12th: September 30, 2017

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reasonOf the patients from whom CRF was not obtained, output details in case other reason is applicable to a patient. Example) personal reason of a patient

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown/not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown

Item	Category
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown

Item	Category
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs*3*4	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual patient

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

For patients experiencing adverse drug reactions after either initial administration or re-administration 1, the presence or absence of adverse drug reactions after the initial administration and initial re-administration,

adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value of test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured values at each time point.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (3) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

4) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured value at each time point.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial administration alone and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in “(7) Other arrangements 5) Data of evaluation time point”.

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration

data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (3), and analyses similar to those described in "7) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

In case only "no pain" or "presence of pain" is recorded as evaluation finding after administration without recording of "improved", "no change", or "worsened", evaluation will be made as follows.

Baseline	Post-dose	Evaluation
No pain	No pain	No change
No pain	Presence of pain	Worsened
Presence of pain	No pain	Improved
Presence of pain	Presence of pain	Not evaluable

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (4) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (4) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Version 2.3: prepared on April 5, 2013

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.3

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number
Ver. 2.3	April 5, 2013	• 4.(1) change in Data Lock Point • 5.(7)5) addition of the following data at evaluation time point: i) acceptable range at each time point; ii) data of Nth administration when a patient received (N+1)th administration.

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) Patients with all efficacy measures unknown

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: September 30, 2013

9th: March 31, 2014

10th: September 30, 2014

11th: September 30, 2015

12th: September 30, 2016

13th: September 30, 2017

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reason.

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of

Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in (Note) 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown/not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown

Item	Category
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown

Item	Category
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*3*4]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual patient

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

For patients experiencing adverse drug reactions after either initial administration or re-administration 1, the presence or absence of adverse drug reactions after the initial administration and initial re-administration,

adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value of test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured values at each time point.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (3) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

4) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value for test results will be shown. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured value at each time point.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial

administration alone and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (3). Analyses similar to those described in 4) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers.

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in “(7) Other arrangements 5) Data of evaluation time point”.

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (3), and analyses similar to those described in "7) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

i) Acceptance range for each time point

The value measured at each point will be the data measured within the acceptable range shown in Table (4) when performing "(5) Efficacy analysis".

ii) Data of Nth administration when administration was conducted for (N+1) times

Of the data of Nth administration recorded in CRF, the data obtained prior to the date of administration of (N+1) times will be used

Table (4) Acceptance range for each time point

Time point	Acceptable range	Standard
Baseline	-28 – 3 days	Day 1 (date of starting administration of this drug)
Week 4	4 – 42 days	28 days

Time point	Acceptable range	Standard
Week 8	43 – 70 days	56 days
Week 12	71 – 126 days	84 days
Week 24	127 – 210 days	168 days
Week 36	211 – 294 days	252 days
Week 48	295 – 420 days	336 days
Final evaluation point	4 – 420 days	-

In case several efficacy data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on “administration category” of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Version 2.2: prepared on July 19, 2011

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.2

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.
Ver. 2.2	July 19, 2011	• 5.(4)1) addition of administration category and administration period category to a list of onset of adverse drug reactions/ infections • 5.(4)3) addition of administration category and administration period category to a list of seriousness, date of onset, outcome • Table (2) addition of "age 2" to patient demographics, addition of "administration period 2", addition of "unknown" to "age" category. • Table (2) change in category of "administration period (cumulative)" in patient demographics • 5.(4)7) addition of comparison of adverse drug reaction profile after the

Version No.	Date of preparation/revision	Site/reason for change
		initial administration and re-administration 1 in individual patients. • 5.(4)8) addition of summary of re-administration intervals • 5.(5)1) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in patients who received re-administration, of summary of initial administration and transition in re-administered patients, and of a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in excess serum ALP. • 5.(5)3) addition of changes in excess serum ALP (subgroup analysis 2) • 5.(5)4) addition of creation of a graph showing changes in percent change and a graph showing changes over time in each patient, of a graph showing changes over time by number of administration in re-administered patients, a summary of initial administration and transition in re-administered patients, and a comparison table of measured values at the initial administration and re-administration 1 and percent change to changes in serum ALP • 5.(5)6) addition of changes in serum ALP (subgroup analysis 2) • 5.(8)7) addition of handling of re-administered patients • 5.(8)8) addition of calculation method for re-administration intervals • 5. overall, renumbering of Form number

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) Patients with all efficacy measures unknown

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reason.

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of

Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Prepare a list of onset of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days) in the same manner shown in Attachment form 2.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in Note 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Prepare a list of adverse drug reactions according to administration category and treatment period (≤56 days, ≥57 days, unknown) in the same manner.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown 7) not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown

Item	Category
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest, 9) unknown * The youngest and oldest ages will be presented as actual values.
Age 2	1) <65 years, 2) ≥65 years, 3) unknown
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Administration category	1) Initial administration, 2) re-administration
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown
Dosing period 2	1) ≤56 days, 2) ≥57 days, 3) unknown, 4) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown

Item	Category
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs*3*4	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

7) Comparison of profiles of adverse drug reactions after initial administration and the initial re-administration in individual patient

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

For patients experiencing adverse drug reactions after either initial administration or re-administration 1, the presence or absence of adverse drug reactions after the initial administration and initial re-administration,

adverse drug reaction name (SOC, PT), seriousness, number of days up to onset of adverse drug reactions, and outcome will be recorded for each patient.

8) Summary of interval of re-administration

<Analysis population>

Patients included in the safety evaluation set who receive re-administration.

<Preparation method>

Summary statistics will be calculated for number of days from the date of completion of the previous administration (date of completion of initial administration in case of re-administration 1) up to the date of starting re-administration according to the number of re-administration.

Handling of re-administration and calculation of interval of re-administration are shown in section "(7) Other arrangements".

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value of test results will be shown.

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured values at each time point.

A graph showing changes over time will be prepared for excess serum ALP up to Week 48 and percent change from baseline in each patient. A graph showing changes over time will be prepared to compare the initial administration in patients without the initial administration in patients who received re-administration. Also, a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

For the data at initial administration in patients who received re-administration, the measured data at each time point and percent change from baseline will be calculated, and summary statistics will be shown. A paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Also, changes in measured data at each time point and percent change from baseline will be shown for each patient.

For each of patients who receive re-administration, measured data at the initial administration and re-administration 1 and percent change from baseline will be compared in the same chart and the same graph.
A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3):

Table (3) Allowable Time Window at Each Assessment t Time Point

Assessment time point	Allowable time window	Standard
Baseline	−28 to 3 days	1 day (day of the initial dose)
Week 4	4 to 42 days	28 days
Week 8	43 to 70 days	56 days
Week 12	71 to 126 days	84 days
Week 24	127 to 210 days	168 days
Week 36	211 to 294 days	252 days
Week 48	295 to 420 days	336 days
Final assessment	4 to 420 days	-

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (4) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in excess serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in excess serum ALP and the percent change at initial administration and re-administration 1 will be compared with the same figure, table, and graph.

4) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value for test results will be shown.

Graphs showing changes in the mean and the percent change from baseline will be prepared for the measured value at each time point.

A graph showing changes over time will be prepared for serum ALP up to Week 48 and percent change from baseline in all patients. A graph showing changes over time will be prepared for patients who received initial administration alone and at initial administration in patients who received re-administration, and a graph showing changes over time will be prepared for re-administration 1 and subsequent administration in patients who received re-administration.

Measured value at each time point and percent change from baseline will be calculated for initial administration in patients who received re-administration, and summary statistics will be shown. Paired t-test will be conducted for differences between pre- and post-dose values and p-value will be shown for the test result. Measured value at each time point and changes in percent change from baseline will be shown for each patient.

Measured value at each time point and percent change from baseline for initial administration and re-administration 1 will be compared in the same figure and the same graph for each patient who receives re-administration.

A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3).

5) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 3) Changes in serum ALP in (5) Efficacy analysis will be performed.

6) Changes in serum ALP (subgroup analysis 2)

<Analysis population>

Patients included in the efficacy evaluation set and who receive re-administration. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Changes in serum ALP and the percent change at initial administration and re-administration 1 will be

compared with the same figure, table, and graph.

7) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3).

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in "(7) Other arrangements 6) Data of evaluation time point".

8) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (4), and analyses similar to those described in "5) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

9) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 6) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

10) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration

data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 6 Data of evaluation time point".

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

In case several serum ALP, bone metabolism marker, pain, and imaging data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become "0" when calculating percent change 4). When excess serum ALP becomes "0", calculate the value as "0.01".

7) Handling of patients who receive re-administration

Initial administration and re-administration will be judged based on "administration category" of CRF.

Whether or not the same patient has received re-administration will be judged based on the information on re-administration separately managed. When a patient has received several re-administrations, arrange them in a temporally order and number them re-administration 1 and 2 starting with the earliest date.

8) Calculation method for intervals of re-administration

Calculate number of days from the date of completion of previous administration (date of completion of administration for the initial administration in case of re-administration 1) up to the date of starting administration.

interval of re-administration = date of administration of this drug - date of completion of previous administration of this drug

Version 2.1: prepared on April 1, 2011

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.1

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"
Ver. 2.1	April 1, 2011	• Table (2) "presence or absence of concomitant drug for osseous Paget's disease" and "other concomitant drugs" were combined as "concomitant drugs". The same for breakdown. • 5.(5)8) deletion of test of imaging diagnosis. • 5.(7)3) deletion of conversion method for days.

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) Patients with all efficacy measures unknown

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reason.

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.Cumulative total and total section in Note 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category

in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown 7) not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest * The youngest and oldest ages will be presented as actual values.
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 84 days,3) 85 to 180 days,4) 181 to 360 days,5) ≥361 days,6) unknown,7) date of onset of adverse drug reactions unknown
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown

Item	Category
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period[*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history[*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity[*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease[*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown
Concomitant drugs	1) none, 2) present, 3) unknown
Details of concomitant drugs[*3*4]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3) Summary statistics will be calculated. Paired t-test will be conducted for differences between pre- and post-dose values and a graph showing changes in mean ± standard deviation over time will be prepared.Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Table (3) Allowable Time Window at Each Assessment t Time Point

Assessment time point	Allowable time window	Standard
Baseline	−28 to 3 days	1 day (day of the initial dose)
Week 4	4 to 42 days	28 days
Week 8	43 to 70 days	56 days
Week 12	71 to 126 days	84 days
Week 24	127 to 210 days	168 days
Week 36	211 to 294 days	252 days
Week 48	295 to 420 days	336 days
Final assessment	4 to 420 days	-

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (4) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3).

Summary statistics will be calculated, and Paired t-test will be conducted for differences between pre- and post-dose values and a graph showing changes in mean ± standard deviation over time will be prepared. Details of handling of data at each time point will be shown in "(7) Other arrangements6) Data of evaluation time point".

4) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 3) Changes in serum ALP in (5) Efficacy analysis will be performed.

5) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3).

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in "(7) Other arrangements6) Data of evaluation time point".

6) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (4), and analyses similar to those described in "5) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

7) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 6) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

8) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration

data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for bone morphology and trabecular bone structure by imaging findings (simple X-ray) at each time point. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 6 Data of evaluation time point".

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

4) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

5) Data at each evaluation time point

In case several serum ALP, bone metabolism marker, pain, and imaging data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

6) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 4). When excess serum ALP becomes “0”, calculate the value as “0.01”.

Version 2.0: prepared on July 7, 2010

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 2.0

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation
Ver. 2.0	July 7, 2010	• Addition of efficacy analysis • Addition of 7.(7) "Excess serum ALP"

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) Patients with all efficacy measures unknown

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reason.

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in Note 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category

in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown 7) not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest * The youngest and oldest ages will be presented as actual values.
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown

Item	Category
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period [*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication [*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history [*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity [*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease [*3]	1) calcitonin preparation, 2)etidronate, 3) this drug (Benet, Actonel), 4) bisphosphonate other than this drug, 5) unknown
Concomitant drugs for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of concomitant drugs for osseous Paget's disease	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other
Other concomitant drugs	1) none, 2) present, 3) unknown
Details of other concomitant drugs [*3*4]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

(5) Efficacy analysis

1) Changes in excess serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, patients without baseline data or post-administration data will be excluded.

<Preparation method>

For excess serum ALP, measured value at each time point and percent change from baseline will be calculated. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

Table (3) Allowable Time Window at Each Assessment t Time Point

Assessment time point	Allowable time window	Standard
Baseline	−28 to 3 days	1 day (day of the initial dose)
Week 4	4 to 42 days	28 days
Week 8	43 to 70 days	56 days
Week 12	71 to 126 days	84 days

Week 24	127 to 210 days	168 days
Week 36	211 to 294 days	252 days
Week 48	295 to 420 days	336 days
Final assessment	4 to 420 days	-

2) Changes in excess serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Excess serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 1) Changes in excess serum ALP in (5) Efficacy analysis will be performed.

Table (4) Stratified categories

Item	Category
Sex	1) F, 2) M
Age	1) <65 years, 2) ≥65 and <75 years, 3) ≥75 years
Administration category	1) initial, 2) re-administration
Prior medication for osseous Paget's disease	1) No, 2) Yes
Prior administration of bisphosphonate product[*1]	1) No, 2) Yes
Concomitant medication for osseous Paget's disease	1) No, 2) Yes

*1: Classify according to the JAPIC Code (drug data file)

3) Changes in serum ALP

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP measured at each time point and percent change from baseline will be calculated. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3).

Summary statistics will be calculated, and Paired t-test will be conducted for differences between pre- and post-dose values. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

4) Changes in serum ALP (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Serum ALP will be stratified by the items shown in Table (4). Analyses similar to those described in 3) Changes in serum ALP in (5) Efficacy analysis will be performed.

5) Changes in bone metabolism markers

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

Measured value at each time point and percent change from baseline will be calculated for each item of bone metabolism markers. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3).

Summary statistics will be calculated, paired t-test will be conducted for differences between pre- and post-dose values. A graph showing changes over time in mean ± standard deviation will be prepared. Details of handling of data at each time point will be shown in "(7) Other arrangements 5) Data of evaluation time point".

6) Changes in bone metabolism markers (subgroup analysis)

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

For bone metabolism markers, patients will be stratified according to the items listed in Table (4), and analyses similar to those described in "5) Changes in bone metabolism markers" in "(5) Efficacy analysis" will be performed.

7) Evaluation of pain associated with osseous Paget's disease

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table will be prepared for evaluation of pain associated with osseous Paget's disease before and after administration at each evaluation time point. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 6) Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in severity of pain before and after administration.

Severity of pain will be scored as shown below prior to analysis.

no pain →0, not disturbing →1, tolerable →2, unbearable →3

8) Imaging findings

<Analysis population>

Patients included in the efficacy evaluation set. However, a patient without baseline or post-administration data will be excluded.

<Preparation method>

A cross-tabulation table before and after administration will be prepared for imaging findings (simple X-ray) at each time point. A measured value at each time point is defined as the one obtained within the allowable time window shown in Table (3). Details of handling of data at each time point will be shown in "(7) Other arrangements 6 Data of evaluation time point".

Bowker's test of symmetry will be conducted for changes in assessment findings before and after administration.

(6) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(7) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

2) Date of starting administration of this drug

The earliest date of [details of treatment] recorded in CRF will be the date of starting administration of this drug.

3) Method of day conversion

- One week consists of 7 days for the purpose of calculation.

- One month consists of 30 days for the purpose of calculation.

4) Summary statistics

Summary statistics will be obtained for number of patients, mean, standard deviation, minimum, Q1, median, Q3, and maximum.

For display of digit, the original data of mean, standard deviation, Q1, median, Q3 will be rounded up to the first decimal place. The minimum and maximum will be shown in digit of original data.

5) Percent change

Percent change will be calculated as follows.

percent change = (measured value after administration – measured value at baseline)/measured value at baseline × 100

6) Data at each evaluation time point

In case several serum ALP, bone metabolism marker, pain, and imaging data exist for the same time point, proceed as shown below.

1) Select the data on the day closest to the standard date.
2) In case there are more than one data with the same number of days before or after the standard date, select the data after the standard date. However, select the data before the date of administration of this drug when time point is baseline.

7) Excess serum ALP

Excess serum ALP will be calculated as follows.

excess serum ALP = measured value of serum ALP - (maximum reference value + minimum reference value)/2

However, denominator may become “0” when calculating percent change 5). When excess serum ALP becomes “0”, calculate the value as “0.01”.

Version 1.3: prepared on April, 9, 2010

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 1.3

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of patients excluded from safety data analysis and patients excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.
Ver. 1.3	April 9, 2010	Revision for the fourth periodic safety report. • Change of terms (change from patients included in safety data analysis to patients included in safety evaluation, patients included in efficacy data analysis to patients included in efficacy evaluation) • 5.(4)3) addition of a list of seriousness, date of onset, outcome of adverse drug reactions • 5.(4)4) addition of onset of adverse drug reactions by patient demographics • 5.(4)5) addition of a list of onset of adverse drug reactions by patient demographics • 5.(4)6) addition of a list of seriousness, date of onset, outcome of adverse drug reactions by patient demographics • 5. (5) addition of analysis of patients excluded from safety evaluation

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Patients included in the safety evaluation set" and "patients included in the efficacy evaluation set".

(2) Patients included in the safety evaluation set

The patients who complete the follow-up and preliminarily fixed after approval at the patient level and do not meet the following conditions are included in the safety evaluation set.

i) A patient not administered this drug

ii) A patient in whom onset of adverse event is unknown

iii) A patient found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Patients included in the efficacy evaluation set

Of the patients included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy evaluation set.

i) Patients with all efficacy measures unknown

3. Handling of patients and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Patient composition diagram

1) number of study sites enrolling patients
2) number of enrolled patients
3) number of patients from whom CRF was collected
4) number of patients included in safety evaluation
5) number of patients included in efficacy evaluation
6) Tabulate the number of "patients from whom CRF was not obtained," "patients excluded from safety evaluation," and "patients excluded from efficacy evaluation" by reason.

(2) Details of patients excluded from safety evaluation and patients excluded from efficacy evaluation

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration of this drug, presence or absence of adverse event, and name of adverse events in order of patient number.

(3) Details of discontinued/dropout patients

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration of this drug, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of patient number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.Cumulative total and total section in Note 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

3) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Tabulate seriousness, date of onset, and outcome of adverse drug reactions by types according to the category

in the following table (1). Adverse drug reactions will be handled according to the "1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". However, in case of several occurrences of adverse drug reactions classified into the same PT in a given patient, select the most serious for seriousness, initial onset for the date of onset of adverse drug reactions, and the severest outcome.

Table (1) Category of seriousness, date of onset, and outcome

Item	Category
Seriousness	1) serious, 2) non-serious, 3) unknown/not provided
Time to onset of adverse drug reactions (day)[*1]	1) Day 1 - 7, 2) Day 8 - 14, 3) Day 15 - 21, 4) Day 22 - 28, 5) Day 29 - 56, 6) Day 57 - 84, 7) Day 85 - 180, 8) Day 181 and thereafter, 9)) unknown/not provided
Outcome	1) recovered, 2) improved, 3) not recovered, 4) recovered with sequela, 5) death, 6) unknown 7) not provided

*1: number of days counted from the "date of starting administration" as "Day 1" until "date of onset of adverse drug reactions".

4) Onset of adverse drug reactions by background factors

Number of patients surveyed, number of patients with onset of adverse drug reactions, percentage (%), and number of occurrences of adverse drug reactions will be tabulated according to the patient demographics shown in Table (2). Presence or absence of adverse drug reactions will be tested according to the patient demographics to investigate the factor that affects safety.

Fisher's exact test will be used for 2×2 contingency table for comparison of categorical data whereas Cochran-Armitage test will be used for 2×c contingency table for ordinal categorical data.

P values will be rounded off to three decimal places. Data reported as "unknown/not provided" will be excluded from tests.

Table (2) Patient demographics

Item	Category
Sex	1) M, 2) F, 3) unknown
Pregnancy (only for women)	1) not pregnant, 2) pregnant, 3) unknown
Age	1) youngest to 29 years, 2) 30 to 39 years, 3) 40 to 49 years, 4) 50 to 59 years, 5) 60 to 69 years, 6) 70 to 74 years, 7) 75 to 79 years, 8) 80 years to oldest * The youngest and oldest ages will be presented as actual values.
Weight	1) <40 kg, 2) ≥40 kg and <50 kg, 3) ≥50 kg and <60 kg, 4) ≥60 kg and <70 kg, 5) ≥70 kg, 6) not measured (unknown)
Dosing period (cumulative) [*1]	1) ≤28 days, 2) ≥29 to 56 days, 3) 57 to 84 days, 4) 85 to 180 days, 5) 181 to 360 days, 6) ≥361 days, 7) unknown, 8) date of onset of adverse drug reactions unknown

Item	Category
Treatment category [*1]	1) outpatient, 2) outpatient ⇔ inpatient, 3) inpatient, 4) inpatient ⇔ outpatient, 5) unknown
Diagnosis name (osseous Paget's disease)	1) monostotic, 2) polyostotic, 3) non-classifiable/ unknown
Diagnosis name (affected site)	1) cranium, 2) vertebrae, 3) pelvis, 4) femur, 5) tibia, 6) other
Morbid period [*2]	1) <1 year, 2) ≥1 and <5 years, 3) ≥5 years, 4) unknown
Complication	1) none, 2) present, 3) unknown
Details of complication [*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Medical history	1) none, 2) present, 3) unknown
Details of medical history [*3*4]	1) hypertension, 2) diabetes mellitus, 3) hepatic disease, 4) cardiac disease, 5) renal disease, 6) gastrointestinal disease, 7) other
Hypersensitivity	1) none, 2) present, 3) unknown
Details of hypersensitivity [*3]	1) drug, 2) food, 3) other, 4) unknown
Family history of osseous Paget's disease	1) none, 2) present, 3) unknown
Details of family history of osseous Paget's disease [*3]	1) father, 2) mother, 3)other, 4) unknown
History of fracture at the affected site	1) none, 2) present, 3) unknown
History of drug therapy for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of history of drug therapy for osseous Paget's disease [*3]	1) calcitonin preparation, 2) etidronate, 3) this drug (Benet), 4) bisphosphonate other than this drug, 5) unknown
Concomitant drugs for osseous Paget's disease	1) none, 2) present, 3) unknown
Details of concomitant drugs for osseous Paget's disease	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other
Other concomitant drugs	1) none, 2) present, 3) unknown
Details of other concomitant drugs [*3*4]	1) osteoporosis agents, 2) anti-inflammatory analgesic, 3) cardiac medication, 4) CNS agents, 5) diabetes medication, 6) gastrointestinal medication, 7) other

*1: No test will be performed for the dosing period because data will be tabulated cumulatively. No test will be performed for the treatment category.

*2: morbid period starts on the "day of initial diagnosis of osteoporosis" and ends on the "day of starting administration of this drug".

*3: tabulate for each category (duplicate tabulation)

*4: classify according to the JAPIC Code (drug data file)

5) List of the onset of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and each adverse drug reaction will be tabulated according to "2) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification from director of MHLW)". Factors will be compared between categories according to the types of adverse drug reaction (SOC [system organ class] of MedDRA). However, Data reported as "unknown/not provided" will be excluded from tests.

6) List of seriousness, date of onset, outcome of adverse drug reactions by patient background factor

<Analysis population>

Patients included in the safety evaluation set.

<Preparation method>

Patients will be stratified according to factors in the above table (2) that show significant differences ($p<0.05$) for the onset/non-onset of adverse drug reactions in the analyses described in "4) Onset of adverse drug reactions by background factors," and analyses similar to those described in "3) List of seriousness, date of onset, outcome of adverse drug reactions" will be performed.

(5) Analysis of patients excluded from safety evaluation

1) List of onset of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "1) List of onset of adverse drug reactions/infections (Attachment form 2 of notification from director of MHLW)" in "(4) Safety analysis" will be conducted. However, total results from the first reporting up to this report will be combined instead of tabulation for each timing.

2) List of seriousness, date of onset, outcome of adverse drug reactions

<Analysis population>

Patients excluded from safety evaluation.

<Preparation method>

Analysis shown in "3) List of seriousness, date of onset, outcome of adverse drug reactions" in "(4) Safety analysis" will be conducted.

(6) Other arrangements

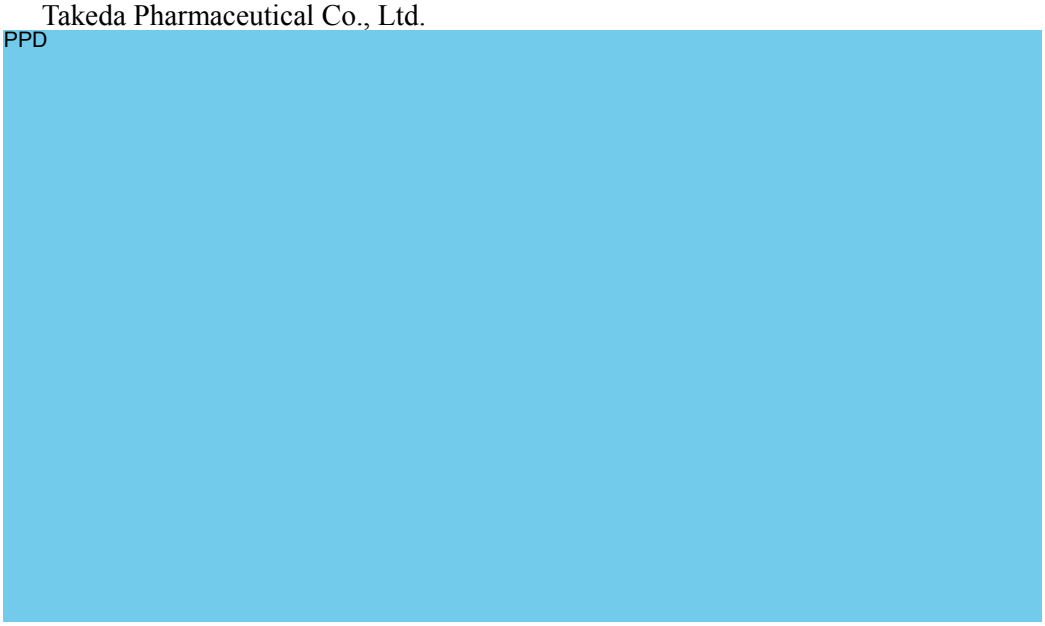
1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 1.2

Takeda Pharmaceutical Co., Ltd.
PPD



Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of subjects excluded from safety data analysis and subjects excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".
Ver. 1.2	September 16, 2009	Revision for the third periodic safety report. • Correction of the date of reexamination in 4. Data Lock Point.

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Subjects included in the safety analysis set" and "subjects included in the efficacy analysis set".

(2) Subjects included in the safety analysis set

The subjects who complete the follow-up and preliminarily fixed after approval at the subject level and do not meet the following conditions are included in the safety analysis n set.

i) A subject not administered this drug

ii) A subject in whom onset of adverse event is unknown

iii) A subject found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Subjects included in the efficacy analysis set

Of the subjects included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy analysis set.

i) subjects with all efficacy measures unknown

3. Handling of subjects and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

The date of re-examination: July 15, 2018

5. Tabulation and analysis at each DLP

(1) Subject composition diagram

1) number of study sites enrolling subjects
2) number of enrolled subjects
3) number of subjects from whom CRF was collected
4) number of subjects included in the safety analysis set
5) number of subjects included in the efficacy analysis set
6) Tabulate the number of "subjects from whom CRF was not obtained," "subjects excluded from the safety analysis set," and "subjects excluded from the efficacy analysis set" by reason.

(2) Details of subjects excluded from the safety analysis set and subjects excluded from the efficacy analysis set

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration, presence or absence of adverse event, and name of adverse events in order of subject number.

(3) Details of discontinued/dropout subjects

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of subject number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of

Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Subjects included in the safety analysis set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Subjects included in the safety analysis set.

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005. Cumulative total and total section in Note 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

(4) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

Version 1.1: prepared on April 8, 2009

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 1.1

Takeda Pharmaceutical Co., Ltd.
PPD

Change history

Version No.	Date of preparation/revision	Site/reason for change
Ver. 1.0	September 25, 2008	New creation
Ver. 1.1	April 8, 2009	Revision for the second periodic safety report. • 5.(2) Addition of "Details of subjects excluded from safety data analysis and subjects excluded from efficacy data analysis". Rearrangement of subsequent section numbers. • Addition of <target of analysis> to 5.(4) 1),2) • 5.(5) Change of section title to "other arrangements".

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg/Actonel Tablet 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Subjects included in the safety analysis set" and "subjects included in the efficacy analysis set".

(2) Subjects included in the safety analysis set

The subjects who complete the follow-up and preliminarily fixed after approval at the subject level and do not meet the following conditions are included in the safety analysis n set.

i) A subject not administered this drug

ii) A subject in whom onset of adverse event is unknown

iii) A subject found to violate the enrollment criteria after preliminary data lock

- Enrollment outside the enrollment period*

(3) Subjects included in the efficacy analysis set

Of the subjects included in the safety evaluation set, those who do not meet the following conditions are excluded from efficacy evaluation and others are included in the efficacy analysis set.

i) subjects with all efficacy measures unknown

3. Handling of subjects and data entry rules

Data entry rules and the handling of patients/data will be specified in a separately prepared document.

4. Data Lock Point

(1) Data Lock Point

Data Lock Points (DLP) are shown below.

1st: September 30, 2008

2nd: March 31, 2009

3rd: September 30, 2009

4th: March 31, 2010

5th: March 31, 2011

6th: March 31, 2012

7th: March 31, 2013

8th: March 31, 2014

9th: March 31, 2015

10th: March 31, 2016

11th: March 31, 2017

12th: March 31, 2018

Re-evaluation: July 31, 2018

5. Tabulation and analysis at each DLP

(1) Subject composition diagram

1) number of study sites enrolling subjects
2) number of enrolled subjects
3) number of subjects from whom CRF was collected
4) number of subjects included in the safety analysis set
5) number of subjects included in the efficacy analysis set
6) Tabulate the number of "subjects from whom CRF was not obtained," "subjects excluded from the safety analysis set," and "subjects excluded from the efficacy analysis set" by reason.

(2) Details of subjects excluded from the safety analysis set and subjects excluded from the efficacy analysis set

Prepare a list of safety evaluation, efficacy evaluation, reason for exclusion, sex, age, date of starting administration, presence or absence of adverse event, and name of adverse events in order of subject number.

(3) Details of discontinued/dropout subjects

Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of subject number.

(4) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of

Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Subjects included in the safety analysis set.

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
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Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

- Calculate percentage (%) for the number of patients by types (occurrences) to the second decimal place (round up to the second decimal place). The same is applied hereinafter unless otherwise stated.

2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Analysis population>

Subjects included in the safety analysis set.

<Preparation method>

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- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

(4) Other arrangements

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.

Version 1.0: prepared on September 25, 2008

Benet 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
Actonel 17.5 mg Tablets Special Drug Use Surveillance in Patients With Osseous Paget's Disease (All-case Surveillance)
- 48-week surveillances-

Statistical Analysis Plan Version 1.0

Takeda Pharmaceutical Co., Ltd.
PPD

Table of Contents

1. Purpose of analysis

To determine tabulation and analysis that are conducted for periodic safety reporting in the survey conducted for the following purpose.

[Purpose of survey]

To observe the efficacy and safety of BENET Tablets 17.5 mg in patients with osseous Paget's disease up to Week 48 as an all-case surveillance based on the approval conditions.

2. Patients to be included in analyses

(1) Breakdown of patients to be included in analyses

"Subjects included in the safety analysis set" and "subjects included in the efficacy analysis set".

(2) Subjects included in the safety analysis set

The subjects who complete the follow-up and preliminarily fixed after approval at the subject level and do not meet the following conditions are included in the safety analysis n set.

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- Enrollment outside the enrollment period*

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Re-evaluation: July 31, 2018

5. Tabulation and analysis at each DLP

(1) Subject composition diagram

1) number of study sites enrolling subjects
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Prepare a list of reason for discontinuation/dropout, safety evaluation, efficacy evaluation, sex, age, date of starting administration, date of discontinuation/dropout, presence or absence of adverse event, and name of adverse events in order of subject number.

(3) Safety analysis

1) List of onset of adverse drug reactions/infections (Attachment form 2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Preparation method>

Prepare according to (Note) 1 to 7 in Attachment form 2 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.

Accumulation and total section in (Note) 2

- The same site participating in Ph 2 and Ph 3 is counted once concerning the number of surveyed sites up to approval.
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- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

Infections in (Note) 7

- No infection was collected or reported by the time of obtaining approval.

Percentage (%) of number of onset (occurrence) of adverse drug reactions by types in (Note) 7

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2) List of occurrences of serious adverse events (Attachment form 2-2 of the notification of Director of Ministry of Health, Labour and Welfare)

<Preparation method>

Prepare according to (Notes) 1 to 8 in Attachment form 10 of PFSB/ELD Notifications Nos. 0325006 and 0325001 of Directors of Pharmaceutical Evaluation and Safety Divisions dated March 25, 2005.Cumulative total and total section in Note 3

- The same site that participates in Ph 2 and Ph 3 studies is counted once concerning the number of surveyed sites up to approval.
- A report submitted by the same site for the first and second reporting is counted once concerning cumulative total section for the number of surveyed sites.
- A report submitted from the same site prior to approval and during a special drug use survey is counted once concerning a total section of a number of surveyed sites.

(4) Other

1) Calculation method for age

Age at last birthday on the date of starting administration of this drug.