



Title: Specified Drug-Use Survey (“Long-Term Use Survey”) on Zacras Combination Tablets LD & HD

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

Protocol for Specified Drug-Use Survey
Specified Drug-Use Survey (“Long-Term Use Survey”)
on Zacras Combination Tablets LD & HD

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Table of Contents

1.0	Background	4
2.0	Objectives.....	4
3.0	Planned Sample Size and Rationale	4
3.1	Planned Sample Size	4
3.2	Rationale.....	4
4.0	Survey Population	5
4.1	Exclusion Criteria.....	5
5.0	Dosage and Administration	5
6.0	Planned Number of Medical Institutions by Department.....	6
7.0	Methods.....	6
7.1	Observation Period.....	6
7.2	Request to and Contract with the Study Site	6
7.3	Method of Patient Registration.....	6
7.4	Completion and Submission of Case Report Form	7
7.5	Actions to be Taken in Case of Serious Adverse Events	7
8.0	Planned Period.....	7
9.0	Survey Items.....	7
9.1	Entries into the Patient Registration Form	7
9.2	Entries into the Case Report Form	8
9.2.1	Cover of the Case Report Form.....	8
9.2.2	Patient Demographics and Baseline Characteristics	8
9.2.3	Treatment Given.....	8
9.2.4	Tests/Observations.....	8
9.2.4.1	Vital Signs	8
9.2.4.2	Laboratory Tests	9
9.2.4.3	Other Observations.....	9
9.2.5	Adverse Events (AEs)	9
10.0	Analysis Items and Methods	11
10.1	Matters on Patient Composition	11
10.2	Patient Demographics and Baseline Characteristics	11
10.3	Treatment Given.....	11
10.4	Matters on Safety	11
10.4.1	Occurrence of Adverse Events	12
10.4.2	Factors that May Affect the Safety.....	12
10.5	Matters on Efficacy	12
10.5.1	Office Blood Pressure.....	12
10.5.2	Factors that May Affect the Efficacy.....	12
11.0	Posting of Survey Information	12
12.0	Organization	12

12.1	Administrative Manager.....	12
12.2	Central Registration Center.....	12
13.0	Contract Research Organization.....	13
14.0	Other Necessary Matters	13
14.1	Revision of the Protocol.....	13
14.2	Actions to be Taken for Problems and Questions.....	13
Appendix Observation schedule.....		14

1.0 Background

Since drugs for hypertension are generally used for a long period of time, the safety of long-term use must be established. While the safety of long-term use of Zacras Combination Tablets LD & HD (hereinafter referred to as Zacras Combination Tablets) was already evaluated in a Japanese Phase III long-term clinical study (duration of treatment: 52 weeks, number of evaluated subjects: 368), it is necessary to evaluate the safety in more patients in clinical settings after marketing, a population that, unlike the study population, receive the drug in diverse situations.

Accordingly, a specified drug-use survey (hereinafter referred to as the survey) is planned to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice. This survey will be conducted in compliance with Good Post-marketing Study Practice (GPSP) ordinance and related requirements.

2.0 Objectives

To evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

1,000 patients

3.2 Rationale

Patient populations identified as important missing information from Japanese clinical studies of Zacras Combination Tablets are patients with renal impairment, patients with hepatic impairment, and elderly patients (≥ 75 years old). The sample size required to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in these patient populations was calculated by reference to previous results. More specifically, according to final tabulation (number of patients included in safety evaluation: 3,300) in a previous specified drug-use survey (long-term use survey in hypertension) of a fixed-dose combination (UNISIA Combination Tablets) of an angiotensin receptor blocker (ARB) (candesartan) and a Ca antagonist (amlodipine), which belongs to the pharmacologically same class as Zacras Combination Tablets, patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 6.9%, 11.5%, and 65.2% (36.8%) of all patients, respectively. According to final tabulation (number of patients included in safety evaluation: 4,152) in a drug use-results survey of candesartan alone (BLOPRESS Tablets), patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 9.5%, 10.6%, and 53.2% (22.1%), respectively. With a target sample size of 1,000 patients for the present survey, 70 patients with renal impairment, 100 patients with hepatic impairment, and 500 elderly patients (and 200 patients ≥ 75 years old)

are expected to be collected, probably allowing the safety and efficacy evaluation in these populations. This calculation is not based on statistical estimation.

4.0 Survey Population

The survey population consists of hypertensive patients who do not meet any of the exclusion criteria listed in Section 4.1. Refer to the “Precautions for Indication” (presented below) and “Precautions” sections in the package insert.

<Precautions for Indication>

Zacras Combination Tablets should not be used as the first-line treatment of hypertension. An excessive drop in blood pressure may occur.

4.1 Exclusion Criteria

Patients who meet any of the following criteria should be excluded from the survey:

- (1) Patients with a history of hypersensitivity to any of the ingredients of Zacras Combination Tablets or other dihydropyridines
- (2) Patients who are or may be pregnant
- (3) Diabetic patients taking aliskiren fumarate (excluding those with markedly poor blood pressure control despite other antihypertensive treatments)

5.0 Dosage and Administration

For adults, one Zacras Combination Tablet (20 mg/2.5 mg or 20 mg/5 mg of azilsartan/amlodipine) will be administered orally once daily. Zacras Combination Tablets should not be used as the first-line treatment of hypertension. Refer to the “Precautions for Dosage and Administration” (presented below) and “Precautions” sections in the package insert.

<Precautions for Dosage and Administration>

- (1) It should be determined whether Zacras Combination Tablets are indicated for each patient individually based on the following Dosage and Administration and Precautions for Dosage and Administration of azilsartan and amlodipine besilate, as well as other relevant information:

Azilsartan

Dosage and Administration

For adults, azilsartan 20 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on age and symptoms, with the maximum daily dose being 40 mg.

Precautions for Dosage and Administration

It should be carefully determined whether or not azilsartan is indicated while keeping the hypotensive effect of azilsartan in mind. Initiation of treatment at a low dose below 20 mg should also be considered.

Amlodipine besilate

•Hypertension

Dosage and Administration

For adults, amlodipine 2.5 to 5 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on symptoms. In the case of insufficient response, the dose may be increased up to 10 mg given once daily.

(2) As a general rule, switching to Zacras Combination Tablets should be considered for patients receiving azilsartan 20 mg with amlodipine 2.5 to 5 mg or patients with poor blood pressure control despite treatment with either one of these treatments.

6.0 Planned Number of Medical Institutions by Department

Internal medicine and other departments	Approximately 250 medical institutions
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7.0 Methods

7.1 Observation Period

12 months

7.2 Request to and Contract with the Study Site

Request and contract for participation in the survey will be made using a paper case report form (CRF). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives, contents, and methods of the survey to the investigator based on "Request for cooperation for specified drug-use survey," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a survey within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration system via fax. After the start of the contract with the study site, the investigator shall register each patient for whom Zacras Combination Tablets are prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 12.2) within 14 days after prescription of Zacras Combination Tablets (day of prescription designated as day 0 and day following the day of prescription designated as 1 day after prescription). No patient can be registered before Zacras Combination Tablets are actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's representative.

Takeda's representative will supply a CRF, which will be issued after the central registration

center decides to register the relevant patient, to the investigator.

7.4 Completion and Submission of Case Report Form

For each of all registered patients, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of the observation period. Any failure to confirm the intake of Zacras Combination Tablets shall be specified (no further information is required).

For patients discontinued from treatment with Zacras Combination Tablets for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of required observation. For any patient discontinued from treatment with Zacras Combination Tablets due to an adverse event, the investigator shall complete and submit a CRF to Takeda Pharmaceutical after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's representative. In addition, the investigator shall provide detailed information at the request of Takeda's representative.

8.0 Planned Period

Survey period: From June 2014 to 31 January 2017

Patient enrollment period: From June 2014 to 31 January 2016^{Note)}

^{Note)} Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 February 2016 onwards even if Zacras Combination Tablets are prescribed by 31 January 2016.

If the number of patients enrolled in the survey reaches the planned sample size before 31 January 2016, acceptance of registration will be terminated before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will be changed accordingly.

9.0 Survey Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The survey schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Survey items

Name of the medical institution, name of a physician who completes the patient registration form, date of prescription of Zacras Combination Tablets, patient identification number, patient initials, sex, date of birth, assessment based on the inclusion criteria, assessment

based on the exclusion criteria, presence or absence of breast-feeding (only females)

2) Time points of survey

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Demographics and Baseline Characteristics

1) Survey items

Time of diagnosis of hypertension, diagnostic category (at the start of treatment with Zacras Combination Tablets), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (presence or absence and details), height, body weight, smoking history, drinking history, presence or absence of breast-feeding (at the start of treatment with Zacras Combination Tablets) [only females]

2) Time points of survey

At the start of treatment with Zacras Combination Tablets

9.2.3 Treatment Given

1) Survey items

Details on the use of Zacras Combination Tablets (daily dose, duration of treatment, and reason for discontinuation of treatment), details on the use of other antihypertensive* (presence or absence, name of the drug, daily dose, and duration of treatment), details on the use of concomitant non-antihypertensive drug (presence or absence, name of the drug, and purpose of use)

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

* Period from 2 months before the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment) for details on the use of other antihypertensive

9.2.4 Tests/Observations

9.2.4.1 Vital Signs

1) Tests/observations

Office blood pressure (systolic/diastolic), pulse rate

2) Time points of survey

Time points of measurement at the start of treatment with Zacras Combination Tablets and after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 months of treatment (or discontinuation of

treatment)

9.2.4.2 Laboratory Tests

1) Test parameters

White blood cell count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), serum creatinine, blood urea nitrogen (BUN), serum potassium

2) Time points of survey

Time points of test from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.4.3 Other Observations

1) Observations

Presence or absence of pregnancy in the observation period (only females)

If pregnancy is detected during the observation period, treatment with Zacras Combination Tablets should be discontinued immediately, and Takeda's representative should be informed. The investigator shall provide detailed information (including information up to delivery such as premature delivery, wherever possible) using a pregnancy sheet at the request of Takeda's representative.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.5 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of treatment with Zacras Combination Tablets, date of outcome assessment, outcome, causal relationship to Zacras Combination Tablets* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

* For the causal relationship to Zacras Combination Tablets, the rationale for "not related" and the reason for "unevaluable" shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE, but expected worsening of target disease should not be handled as an AE.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of

treatment (or discontinuation of treatment)

Table 1 Definition of adverse events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

The following are also handled as AEs:

- Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug
- Symptoms and so forth that occur in children treated with a drug
- Symptoms and so forth that occur as a result of occupational exposure to a drug
- Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs

Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

Takeda Medically Significant AE List

- | | |
|--|---|
| •Acute respiratory failure/acute respiratory distress syndrome (ARDS) | •Anaphylactic shock |
| •Torsade de pointes / ventricular fibrillation / ventricular tachycardia | •Acute renal failure |
| •Malignant hypertension | •Pulmonary hypertension |
| •Convulsive seizures (including convulsion and epilepsy) | •Pulmonary fibrosis (including interstitial pneumonia) |
| •Agranulocytosis | •Neuroleptic malignant syndrome / malignant hyperthermia |
| •Aplastic anemia | •Spontaneous abortion / stillbirth and fetal death |
| •Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome) | •Confirmed or suspected transmission of infectious agent by a medicinal product |
| •Hepatic necrosis | •Confirmed or suspected endotoxin shock |
| •Acute liver failure | |

Table 3 Criteria for assessing the relationship of each adverse event to Zacras Combination Tablets

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients from whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics, including sex, age, duration of disease, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Given

Details on the use of Zacras Combination Tablets, details on the use of other antihypertensive, and details on the use of concomitant non-antihypertensive drug will be tabulated.

10.4 Matters on Safety

For the safety analysis set, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.4.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Zacras Combination Tablets.

10.4.2 Factors that May Affect the Safety

For AEs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., sex, age, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of concomitant drug).

10.5 Matters on Efficacy

For the efficacy analysis set, data will be tabulated as described below.

10.5.1 Office Blood Pressure

For office blood pressure, measured value, change (measured value at each post-baseline time point of measurement - measured value at the start of treatment with Zacras Combination Tablets), and percentage change $[(\text{measured value at each time point of measurement} - \text{measured value at the start of treatment with Zacras Combination Tablets}) \div \text{measured value at the start of treatment with Zacras Combination Tablets} \times 100]$ at each time point of test will be tabulated.

10.5.2 Factors that May Affect the Efficacy

Office blood pressure will be tabulated by patient background factors (e.g., sex, age) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of other antihypertensive).

11.0 Posting of Survey Information

Takeda Pharmaceutical Company Limited will post survey information on Clinical Trials.gov and an open website (JAPIC-CTI*) before starting the survey.

* Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

12.2 Central Registration Center

PPD

13.0 Contract Research Organization

PPD



14.0 Other Necessary Matters

14.1 Revision of the Protocol

During the survey, attention will be paid to comprehend the status of progression of the survey, presence or absence of unexpected adverse drug reactions (ADRs)/serious ADRs (based on precautions), presence or absence of increased incidence of certain ADRs, and appropriateness of survey items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the survey, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

14.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix Observation schedule

Time point of survey Survey item		Observation period														
		At patient registration	Start of treatment	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment	After 4 months of treatment	After 5 months of treatment	After 6 months of treatment	After 7 months of treatment	After 8 months of treatment	After 9 months of treatment	After 10 months of treatment	After 11 months of treatment	After 12 months of treatment	At discontinuation of treatment
Patient registration	Date of prescription of Zacras Combination Tablets	<input type="radio"/>														
	Patient identification number	<input type="radio"/>														
	Patient initials	<input type="radio"/>														
	Sex	<input type="radio"/>														
	Date of birth	<input type="radio"/>														
	Inclusion/exclusion criteria	<input type="radio"/>														
	Presence or absence of breast-feeding (only females)	<input type="radio"/>														
Patient demographics and baseline characteristics	Time of diagnosis of hypertension		<input type="radio"/>													
	Diagnostic category		<input type="radio"/>													
	Predisposition to hypersensitivity		<input type="radio"/>													
	Concurrent illness		<input type="radio"/>													
	Medical history		<input type="radio"/>													
	Height, body weight		<input type="radio"/>													
	Smoking history		<input type="radio"/>													
	Drinking history		<input type="radio"/>													
	Presence or absence of breast-feeding (only females)		<input type="radio"/>													
Treatment given, etc.	Details on the use of Zacras Combination Tablets		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><di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	γ-GTP		←	○	→	○
	Serum creatinine		←	○	→	○
	BUN		←	○	→	○
	Serum potassium		←	○	→	○
	Presence or absence of pregnancy (only females)		←	○	→	○
	Adverse event		←	○	→	○

○ : Performed

← ○ → : Performed throughout the period

Protocol for Specified Drug-Use Survey
Specified Drug-Use Survey (“Long-Term Use Survey”)
on Zacras Combination Tablets LD & HD

Version number	3rd version
Date of preparation	1 April 2015
Sponsor	Takeda Pharmaceutical Company Limited

Table of Contents

1.0	Background	4
2.0	Objectives.....	4
3.0	Planned Sample Size and Rationale	4
3.1	Planned Sample Size	4
3.2	Rationale.....	4
4.0	Survey Population	5
4.1	Exclusion Criteria.....	5
5.0	Dosage and Administration	5
6.0	Planned Number of Medical Institutions by Department.....	6
7.0	Methods.....	6
7.1	Observation Period.....	6
7.2	Request to and Contract with the Study Site	6
7.3	Method of Patient Registration.....	6
7.4	Completion and Submission of Case Report Form	7
7.5	Actions to be Taken in Case of Serious Adverse Events	7
8.0	Planned Period.....	7
9.0	Survey Items.....	7
9.1	Entries into the Patient Registration Form	7
9.2	Entries into the Case Report Form	8
9.2.1	Cover of the Case Report Form.....	8
9.2.2	Patient Demographics and Baseline Characteristics	8
9.2.3	Treatment Given.....	8
9.2.4	Tests/Observations.....	8
9.2.4.1	Vital Signs	8
9.2.4.2	Laboratory Tests	9
9.2.4.3	Other Observations.....	9
9.2.5	Adverse Events (AEs)	9
10.0	Analysis Items and Methods	11
10.1	Matters on Patient Composition	11
10.2	Patient Demographics and Baseline Characteristics	11
10.3	Treatment Given.....	11
10.4	Matters on Safety	11
10.4.1	Occurrence of Adverse Events	11
10.4.2	Factors that May Affect the Safety	12
10.5	Matters on Efficacy	12
10.5.1	Office Blood Pressure.....	12
10.5.2	Factors that May Affect the Efficacy.....	12
11.0	Posting of Survey Information	12
12.0	Organization	12

12.1	Administrative Manager.....	12
12.2	Central Registration Center.....	12
13.0	Contract Research Organizations	12
14.0	Other Necessary Matters	13
14.1	Revision of the Protocol.....	13
14.2	Actions to be Taken for Problems and Questions.....	13
Appendix Observation schedule.....		14

1.0 Background

Since drugs for hypertension are generally used for a long period of time, the safety of long-term use must be established. While the safety of long-term use of Zacras Combination Tablets LD & HD (hereinafter referred to as Zacras Combination Tablets) was already evaluated in a Japanese Phase III long-term clinical study (duration of treatment: 52 weeks, number of evaluated subjects: 368), it is necessary to evaluate the safety in more patients in clinical settings after marketing, a population that, unlike the study population, receive the drug in diverse situations.

Accordingly, a specified drug-use survey (hereinafter referred to as the survey) is planned to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice. This survey will be conducted in compliance with Good Post-marketing Study Practice (GPSP) ordinance and related requirements.

2.0 Objectives

To evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

1,000 patients

3.2 Rationale

Patient populations identified as important missing information from Japanese clinical studies of Zacras Combination Tablets are patients with renal impairment, patients with hepatic impairment, and elderly patients (≥ 75 years old). The sample size required to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in these patient populations was calculated by reference to previous results. More specifically, according to final tabulation (number of patients included in safety evaluation: 3,300) in a previous specified drug-use survey (long-term use survey in hypertension) of a fixed-dose combination (UNISIA Combination Tablets) of an angiotensin receptor blocker (ARB) (candesartan) and a Ca antagonist (amlodipine), which belongs to the pharmacologically same class as Zacras Combination Tablets, patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 6.9%, 11.5%, and 65.2% (36.8%) of all patients, respectively. According to final tabulation (number of patients included in safety evaluation: 4,152) in a drug use-results survey of candesartan alone (BLOPRESS Tablets), patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 9.5%, 10.6%, and 53.2% (22.1%), respectively. With a target sample size of 1,000 patients for the present survey, 70 patients with renal impairment, 100 patients with hepatic impairment, and 500 elderly patients (and 200 patients ≥ 75 years old)

are expected to be collected, probably allowing the safety and efficacy evaluation in these populations. This calculation is not based on statistical estimation.

4.0 Survey Population

The survey population consists of hypertensive patients who do not meet any of the exclusion criteria listed in Section 4.1. Refer to the “Precautions for Indication” (presented below) and “Precautions” sections in the package insert.

<Precautions for Indication>

Zacras Combination Tablets should not be used as the first-line treatment of hypertension. An excessive drop in blood pressure may occur.

4.1 Exclusion Criteria

Patients who meet any of the following criteria should be excluded from the survey:

- (1) Patients with a history of hypersensitivity to any of the ingredients of Zacras Combination Tablets or other dihydropyridines
- (2) Patients who are or may be pregnant
- (3) Diabetic patients taking aliskiren fumarate (excluding those with markedly poor blood pressure control despite other antihypertensive treatments)

5.0 Dosage and Administration

For adults, one Zacras Combination Tablet (20 mg/2.5 mg or 20 mg/5 mg of azilsartan/amlodipine) will be administered orally once daily. Zacras Combination Tablets should not be used as the first-line treatment of hypertension. Refer to the “Precautions for Dosage and Administration” (presented below) and “Precautions” sections in the package insert.

<Precautions for Dosage and Administration>

- (1) It should be determined whether Zacras Combination Tablets are indicated for each patient individually based on the following Dosage and Administration and Precautions for Dosage and Administration of azilsartan and amlodipine besilate, as well as other relevant information:

Azilsartan

Dosage and Administration

For adults, azilsartan 20 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on age and symptoms, with the maximum daily dose being 40 mg.

Precautions for Dosage and Administration

It should be carefully determined whether or not azilsartan is indicated while keeping the hypotensive effect of azilsartan in mind. Initiation of treatment at a low dose below 20 mg should also be considered.

Amlodipine besilate

•Hypertension

Dosage and Administration

For adults, amlodipine 2.5 to 5 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on symptoms. In the case of insufficient response, the dose may be increased up to 10 mg given once daily.

(2) As a general rule, switching to Zacras Combination Tablets should be considered for patients receiving azilsartan 20 mg with amlodipine 2.5 to 5 mg or patients with poor blood pressure control despite treatment with either one of these treatments.

6.0 Planned Number of Medical Institutions by Department

Internal medicine and other departments	Approximately 250 medical institutions
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7.0 Methods

7.1 Observation Period

12 months

7.2 Request to and Contract with the Study Site

Request and contract for participation in the survey will be made using a paper case report form (CRF). A representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's representative) will explain the objectives, contents, and methods of the survey to the investigator based on "Request for cooperation for specified drug-use survey," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a survey within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration system via fax. After the start of the contract with the study site, the investigator shall register each patient for whom Zacras Combination Tablets are prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 12.2) within 14 days after prescription of Zacras Combination Tablets (day of prescription designated as day 0 and day following the day of prescription designated as 1 day after prescription). No patient can be registered before Zacras Combination Tablets are actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's representative.

Takeda's representative will supply a CRF, which will be issued after the central registration

center decides to register the relevant patient, to the investigator.

7.4 Completion and Submission of Case Report Form

For each of all registered patients, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of the observation period. Any failure to confirm the intake of Zacras Combination Tablets shall be specified (no further information is required).

For patients discontinued from treatment with Zacras Combination Tablets for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda Pharmaceutical within approximately 1 month after the end of required observation. For any patient discontinued from treatment with Zacras Combination Tablets due to an adverse event, the investigator shall complete and submit a CRF to Takeda Pharmaceutical after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's representative. In addition, the investigator shall provide detailed information at the request of Takeda's representative.

8.0 Planned Period

Survey period: From June 2014 to 31 January 2017

Patient enrollment period: From June 2014 to 31 January 2016^{Note)}

^{Note)} Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 February 2016 onwards even if Zacras Combination Tablets are prescribed by 31 January 2016.

If the number of patients enrolled in the survey reaches the planned sample size before 31 January 2016, acceptance of registration will be terminated before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will be changed accordingly.

9.0 Survey Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The survey schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Survey items

Name of the medical institution, name of a physician who completes the patient registration form, date of prescription of Zacras Combination Tablets, patient identification number, patient initials, sex, date of birth, assessment based on the inclusion criteria, assessment

based on the exclusion criteria, presence or absence of breast-feeding (only females)

2) Time points of survey

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Demographics and Baseline Characteristics

1) Survey items

Time of diagnosis of hypertension, diagnostic category (at the start of treatment with Zacras Combination Tablets), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (presence or absence and details), height, body weight, smoking history, drinking history, presence or absence of breast-feeding (at the start of treatment with Zacras Combination Tablets) [only females]

2) Time points of survey

At the start of treatment with Zacras Combination Tablets

9.2.3 Treatment Given

1) Survey items

Details on the use of Zacras Combination Tablets (daily dose, duration of treatment, and reason for discontinuation of treatment), details on the use of other antihypertensive* (presence or absence, name of the drug, daily dose, and duration of treatment), details on the use of concomitant non-antihypertensive drug (presence or absence, name of the drug, and purpose of use)

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

* Period from 2 months before the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment) for details on the use of other antihypertensive

9.2.4 Tests/Observations

9.2.4.1 Vital Signs

1) Tests/observations

Office blood pressure (systolic/diastolic), pulse rate

2) Time points of survey

Time points of measurement at the start of treatment with Zacras Combination Tablets and after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 months of treatment (or discontinuation of

treatment)

9.2.4.2 Laboratory Tests

1) Test parameters

White blood cell count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), serum creatinine, blood urea nitrogen (BUN), serum potassium

2) Time points of survey

Time points of test from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.4.3 Other Observations

1) Observations

Presence or absence of pregnancy in the observation period (only females)

If pregnancy is detected during the observation period, treatment with Zacras Combination Tablets should be discontinued immediately, and Takeda's representative should be informed. The investigator shall provide detailed information (including information up to delivery such as premature delivery, wherever possible) using a pregnancy sheet at the request of Takeda's representative.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.5 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of treatment with Zacras Combination Tablets, date of outcome assessment, outcome, causal relationship to Zacras Combination Tablets* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

* For the causal relationship to Zacras Combination Tablets, the rationale for "not related" and the reason for "unevaluable" shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE, but expected worsening of target disease should not be handled as an AE.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of

treatment (or discontinuation of treatment)

Table 1 Definition of adverse events

<p>An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.</p> <p>The following are also handled as AEs:</p> <ul style="list-style-type: none">•Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug•Symptoms and so forth that occur in children treated with a drug· Symptoms and so forth that occur as a result of occupational exposure to a drug· Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs

Table 2 Criteria for assessing seriousness

<p>An AE satisfying any of the following is assessed as serious:</p> <ol style="list-style-type: none">1. Results in death (death)2. Is life-threatening (risk of death)3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)4. Results in persistent or significant disability/incapacity (disability)5. Leads to a congenital anomaly/birth defect (congenital anomaly)6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List	
<p><u>Takeda Medically Significant AE List</u></p>	
•Acute respiratory failure/acute respiratory distress syndrome (ARDS)	•Anaphylactic shock
•Torsade de pointes / ventricular fibrillation / ventricular tachycardia	•Acute renal failure
•Malignant hypertension	•Pulmonary hypertension
•Convulsive seizures (including convulsion and epilepsy)	•Pulmonary fibrosis (including interstitial pneumonia)
•Agranulocytosis	•Neuroleptic malignant syndrome / malignant hyperthermia
•Aplastic anemia	•Spontaneous abortion / stillbirth and fetal death
•Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)	•Confirmed or suspected transmission of infectious agent by a medicinal product
•Hepatic necrosis	•Confirmed or suspected endotoxin shock
•Acute liver failure	

Table 3 Criteria for assessing the relationship of each adverse event to Zacras Combination Tablets

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients from whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics, including sex, age, duration of disease, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Given

Details on the use of Zacras Combination Tablets, details on the use of other antihypertensive, and details on the use of concomitant non-antihypertensive drug will be tabulated.

10.4 Matters on Safety

For the safety analysis set, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.4.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time

of onset, seriousness, and causal relationship to Zacras Combination Tablets.

10.4.2 Factors that May Affect the Safety

For AEs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., sex, age, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of concomitant drug).

10.5 Matters on Efficacy

For the efficacy analysis set, data will be tabulated as described below.

10.5.1 Office Blood Pressure

For office blood pressure, measured value, change (measured value at each post-baseline time point of measurement - measured value at the start of treatment with Zacras Combination Tablets), and percentage change $[(\text{measured value at each time point of measurement} - \text{measured value at the start of treatment with Zacras Combination Tablets}) \div \text{measured value at the start of treatment with Zacras Combination Tablets} \times 100]$ at each time point of test will be tabulated.

10.5.2 Factors that May Affect the Efficacy

Office blood pressure will be tabulated by patient background factors (e.g., sex, age) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of other antihypertensive).

11.0 Posting of Survey Information

Takeda Pharmaceutical Company Limited will post survey information on Clinical Trials.gov and an open website (JAPIC-CTI*) before starting the survey.

* Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organization

12.1 Administrative Manager

PPD

Takeda Pharmaceutical Company Limited

12.2 Central Registration Center

PPD

13.0 Contract Research Organization

PPD

14.0 Other Necessary Matters

14.1 Revision of the Protocol

During the survey, attention will be paid to comprehend the status of progression of the survey, presence or absence of unexpected adverse drug reactions (ADRs)/serious ADRs (based on precautions), presence or absence of increased incidence of certain ADRs, and appropriateness of survey items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the survey, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

14.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix Observation schedule

Time point of survey Survey item		Observation period															
		At patient registration	Start of treatment	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment	After 4 months of treatment	After 5 months of treatment	After 6 months of treatment	After 7 months of treatment	After 8 months of treatment	After 9 months of treatment	After 10 months of treatment	After 11 months of treatment	After 12 months of treatment	At discontinuation of treatment	
Patient registration	Date of prescription of Zacras Combination Tablets	<input type="radio"/>															
	Patient identification number	<input type="radio"/>															
	Patient initials	<input type="radio"/>															
	Sex	<input type="radio"/>															
	Date of birth	<input type="radio"/>															
	Inclusion/exclusion criteria	<input type="radio"/>															
	Presence or absence of breast-feeding (only females)	<input type="radio"/>															
Patient demographics and baseline characteristics	Time of diagnosis of hypertension		<input type="radio"/>														
	Diagnostic category		<input type="radio"/>														
	Predisposition to hypersensitivity		<input type="radio"/>														
	Concurrent illness		<input type="radio"/>														
	Medical history		<input type="radio"/>														
	Height, body weight		<input type="radio"/>														
	Smoking history		<input type="radio"/>														
	Drinking history		<input type="radio"/>														
	Presence or absence of breast-feeding (only females)		<input type="radio"/>														
Treatment given, etc.	Details on the use of Zacras Combination Tablets		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>
	Details on the use of other antihypertensive		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>
	Details on the use of concomitant non-antihypertensive drug		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>
Tests/observations, etc.	Office blood pressure		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
	Pulse rate		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
	White blood cell count		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>
	Platelet count		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>
	AST		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>
	ALT		<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div> <input type="radio"/>														<input type="radio"/>

	γ -GTP		←	○	→	○
	Serum creatinine		←	○	→	○
	BUN		←	○	→	○
	Serum potassium		←	○	→	○
	Presence or absence of pregnancy (only females)		←	○	→	○
	Adverse event		←	○	→	○

○ : Performed

← ○ → : Performed throughout the period

Protocol for Specified Drug-Use Survey
Specified Drug-Use Survey (“Long-Term Use Survey”)
on Zacras Combination Tablets LD & HD

Version number	2nd version
Date of preparation	15 May 2014
Sponsor	Takeda Pharmaceutical Company Limited

Table of Contents

1.0	Background	4
2.0	Objectives.....	4
3.0	Planned Sample Size and Rationale	4
3.1	Planned Sample Size	4
3.2	Rationale.....	4
4.0	Survey Population	5
4.1	Exclusion Criteria.....	5
5.0	Dosage and Administration	5
6.0	Planned Number of Medical Institutions by Department.....	6
7.0	Methods.....	6
7.1	Observation Period.....	6
7.2	Request to and Contract with the Study Site	6
7.3	Method of Patient Registration.....	6
7.4	Completion and Submission of Case Report Form	7
7.5	Actions to be Taken in Case of Serious Adverse Events	7
8.0	Planned Period.....	7
9.0	Survey Items.....	7
9.1	Entries into the Patient Registration Form	7
9.2	Entries into the Case Report Form	8
9.2.1	Cover of the Case Report Form.....	8
9.2.2	Patient Demographics and Baseline Characteristics	8
9.2.3	Treatment Given.....	8
9.2.4	Tests/Observations.....	8
9.2.4.1	Vital Signs	8
9.2.4.2	Laboratory Tests	9
9.2.4.3	Other Observations.....	9
9.2.5	Adverse Events (AEs)	9
10.0	Analysis Items and Methods	11
10.1	Matters on Patient Composition	11
10.2	Patient Demographics and Baseline Characteristics	11
10.3	Treatment Given.....	11
10.4	Matters on Safety	11
10.4.1	Occurrence of Adverse Events	12
10.4.2	Factors that May Affect the Safety.....	12
10.5	Matters on Efficacy	12
10.5.1	Office Blood Pressure.....	12
10.5.2	Factors that May Affect the Efficacy.....	12
11.0	Posting of Survey Information	12
12.0	Organization	12

12.1	Administrative Manager.....	12
12.2	Central Registration Center.....	12
13.0	Contract Research Organization.....	13
14.0	Other Necessary Matters	13
14.1	Revision of the Protocol.....	13
14.2	Actions to be Taken for Problems and Questions.....	13
Appendix Observation schedule.....		14

1.0 Background

Since drugs for hypertension are generally used for a long period of time, the safety of long-term use must be established. While the safety of long-term use of Zacras Combination Tablets LD & HD (hereinafter referred to as Zacras Combination Tablets) was already evaluated in a Japanese Phase III long-term clinical study (duration of treatment: 52 weeks, number of evaluated subjects: 368), it is necessary to evaluate the safety in more patients in clinical settings after marketing, a population that, unlike the study population, receive the drug in diverse situations.

Accordingly, a specified drug-use survey (hereinafter referred to as the survey) is planned to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice. This survey will be conducted in compliance with Good Post-marketing Study Practice (GPSP) ordinance and related requirements.

2.0 Objectives

To evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

1,000 patients

3.2 Rationale

Patient populations identified as important missing information from Japanese clinical studies of Zacras Combination Tablets are patients with renal impairment, patients with hepatic impairment, and elderly patients (≥ 75 years old). The sample size required to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in these patient populations was calculated by reference to previous results. More specifically, according to final tabulation (number of patients included in safety evaluation: 3,300) in a previous specified drug-use survey (long-term use survey in hypertension) of a fixed-dose combination (UNISIA Combination Tablets) of an angiotensin receptor blocker (ARB) (candesartan) and a Ca antagonist (amlodipine), which belongs to the pharmacologically same class as Zacras Combination Tablets, patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 6.9%, 11.5%, and 65.2% (36.8%) of all patients, respectively. According to final tabulation (number of patients included in safety evaluation: 4,152) in a drug use-results survey of candesartan alone (BLOPRESS Tablets), patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 9.5%, 10.6%, and 53.2% (22.1%), respectively. With a target sample size of 1,000 patients for the present survey, 70 patients with renal impairment, 100 patients with hepatic impairment, and 500 elderly patients (and 200 patients ≥ 75 years old)

are expected to be collected, probably allowing the safety and efficacy evaluation in these populations. This calculation is not based on statistical estimation.

4.0 Survey Population

The survey population consists of hypertensive patients who do not meet any of the exclusion criteria listed in Section 4.1. Refer to the “Precautions for Indication” (presented below) and “Precautions” sections in the package insert.

<Precautions for Indication>

Zacras Combination Tablets should not be used as the first-line treatment of hypertension. An excessive drop in blood pressure may occur.

4.1 Exclusion Criteria

Patients who meet any of the following criteria should be excluded from the survey:

- (1) Patients with a history of hypersensitivity to any of the ingredients of Zacras Combination Tablets or other dihydropyridines
- (2) Patients who are or may be pregnant
- (3) Diabetic patients taking aliskiren fumarate (excluding those with markedly poor blood pressure control despite other antihypertensive treatments)

5.0 Dosage and Administration

For adults, one Zacras Combination Tablet (20 mg/2.5 mg or 20 mg/5 mg of azilsartan/amlodipine) will be administered orally once daily. Zacras Combination Tablets should not be used as the first-line treatment of hypertension. Refer to the “Precautions for Dosage and Administration” (presented below) and “Precautions” sections in the package insert.

<Precautions for Dosage and Administration>

- (1) It should be determined whether Zacras Combination Tablets are indicated for each patient individually based on the following Dosage and Administration and Precautions for Dosage and Administration of azilsartan and amlodipine besilate, as well as other relevant information:

Azilsartan

Dosage and Administration

For adults, azilsartan 20 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on age and symptoms, with the maximum daily dose being 40 mg.

Precautions for Dosage and Administration

It should be carefully determined whether or not azilsartan is indicated while keeping the hypotensive effect of azilsartan in mind. Initiation of treatment at a low dose below 20 mg should also be considered.

Amlodipine besilate

•Hypertension

Dosage and Administration

For adults, amlodipine 2.5 to 5 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on symptoms. In the case of insufficient response, the dose may be increased up to 10 mg given once daily.

(2) As a general rule, switching to Zacras Combination Tablets should be considered for patients receiving azilsartan 20 mg with amlodipine 2.5 to 5 mg or patients with poor blood pressure control despite treatment with either one of these treatments.

6.0 Planned Number of Medical Institutions by Department

Internal medicine and other departments	Approximately 250 medical institutions
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7.0 Methods

7.1 Observation Period

12 months

7.2 Request to and Contract with the Study Site

Request and contract for participation in the survey will be made using a paper case report form (CRF). A medical representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's MR) will explain the objectives, contents, and methods of the survey to the investigator based on "Request for cooperation for specified drug-use survey," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a survey within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration system via fax. After the start of the contract with the study site, the investigator shall register each patient for whom Zacras Combination Tablets are prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 12.2) within 14 days after prescription of Zacras Combination Tablets (day of prescription designated as day 0 and day following the day of prescription designated as 1 day after prescription). No patient can be registered before Zacras Combination Tablets are actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's MR.

Takeda's MR will supply a CRF, which will be issued after the central registration center

decides to register the relevant patient, to the investigator.

7.4 Completion and Submission of Case Report Form

For each of all registered patients, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of the observation period. Any failure to confirm the intake of Zacras Combination Tablets shall be specified (no further information is required).

For patients discontinued from treatment with Zacras Combination Tablets for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of required observation. For any patient discontinued from treatment with Zacras Combination Tablets due to an adverse event, the investigator shall complete and submit a CRF to Takeda's MR after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's MR. In addition, the investigator shall provide detailed information at the request of Takeda's MR.

8.0 Planned Period

Survey period: From June 2014 to 31 January 2017

Patient enrollment period: From June 2014 to 31 January 2016^{Note)}

^{Note)} Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 February 2016 onwards even if Zacras Combination Tablets are prescribed by 31 January 2016.

If the number of patients enrolled in the survey reaches the planned sample size before 31 January 2016, acceptance of registration will be terminated before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will be changed accordingly.

9.0 Survey Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The survey schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Survey items

Name of the medical institution, name of a physician who completes the patient registration form, date of prescription of Zacras Combination Tablets, patient identification number, patient initials, sex, date of birth, assessment based on the inclusion criteria, assessment

based on the exclusion criteria, presence or absence of breast-feeding (only females)

2) Time points of survey

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Demographics and Baseline Characteristics

1) Survey items

Time of diagnosis of hypertension, diagnostic category (at the start of treatment with Zacras Combination Tablets), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (presence or absence and details), height, body weight, smoking history, drinking history, presence or absence of breast-feeding (at the start of treatment with Zacras Combination Tablets) [only females]

2) Time points of survey

At the start of treatment with Zacras Combination Tablets

9.2.3 Treatment Given

1) Survey items

Details on the use of Zacras Combination Tablets (daily dose, duration of treatment, and reason for discontinuation of treatment), details on the use of other antihypertensive* (presence or absence, name of the drug, daily dose, and duration of treatment), details on the use of concomitant non-antihypertensive drug (presence or absence, name of the drug, and purpose of use)

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

* Period from 2 months before the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment) for details on the use of other antihypertensive

9.2.4 Tests/Observations

9.2.4.1 Vital Signs

1) Tests/observations

Office blood pressure (systolic/diastolic), pulse rate

2) Time points of survey

Time points of measurement at the start of treatment with Zacras Combination Tablets and after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 months of treatment (or discontinuation of

treatment)

9.2.4.2 Laboratory Tests

1) Test parameters

White blood cell count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), serum creatinine, blood urea nitrogen (BUN), serum potassium

2) Time points of survey

Time points of test from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.4.3 Other Observations

1) Observations

Presence or absence of pregnancy in the observation period (only females)

If pregnancy is detected during the observation period, treatment with Zacras Combination Tablets should be discontinued immediately, and Takeda's MR should be informed. The investigator shall provide detailed information (including information up to delivery such as premature delivery, wherever possible) using a pregnancy sheet at the request of Takeda's MR.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.5 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of treatment with Zacras Combination Tablets, date of outcome assessment, outcome, causal relationship to Zacras Combination Tablets* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

* For the causal relationship to Zacras Combination Tablets, the rationale for "not related" and the reason for "unevaluable" shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE, but expected worsening of target disease should not be handled as an AE.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of

treatment (or discontinuation of treatment)

Table 1 Definition of adverse events

<p>An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.</p> <p>The following are also handled as AEs:</p> <ul style="list-style-type: none"> •Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug •Symptoms and so forth that occur in children treated with a drug •Symptoms and so forth that occur as a result of occupational exposure to a drug •Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
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Table 2 Criteria for assessing seriousness

<p>An AE satisfying any of the following is assessed as serious:</p> <ol style="list-style-type: none"> 1. Results in death (death) 2. Is life-threatening (risk of death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Leads to a congenital anomaly/birth defect (congenital anomaly) 6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List 	
<p><u>Takeda Medically Significant AE List</u></p>	
<ul style="list-style-type: none"> •Acute respiratory failure/acute respiratory distress syndrome (ARDS) •Torsade de pointes / ventricular fibrillation / ventricular tachycardia •Malignant hypertension •Convulsive seizures (including convulsion and epilepsy) •Agranulocytosis •Aplastic anemia •Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome) •Hepatic necrosis •Acute liver failure 	<ul style="list-style-type: none"> •Anaphylactic shock •Acute renal failure •Pulmonary hypertension •Pulmonary fibrosis (including interstitial pneumonia) •Neuroleptic malignant syndrome / malignant hyperthermia •Spontaneous abortion / stillbirth and fetal death •Confirmed or suspected transmission of infectious agent by a medicinal product •Confirmed or suspected endotoxin shock

Table 3 Criteria for assessing the relationship of each adverse event to Zacras Combination Tablets

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients from whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics, including sex, age, duration of disease, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Given

Details on the use of Zacras Combination Tablets, details on the use of other antihypertensive, and details on the use of concomitant non-antihypertensive drug will be tabulated.

10.4 Matters on Safety

For the safety analysis set, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.4.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Zacras Combination Tablets.

10.4.2 Factors that May Affect the Safety

For AEs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., sex, age, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of concomitant drug).

10.5 Matters on Efficacy

For the efficacy analysis set, data will be tabulated as described below.

10.5.1 Office Blood Pressure

For office blood pressure, measured value, change (measured value at each post-baseline time point of measurement - measured value at the start of treatment with Zacras Combination Tablets), and percentage change $[(\text{measured value at each time point of measurement} - \text{measured value at the start of treatment with Zacras Combination Tablets}) \div \text{measured value at the start of treatment with Zacras Combination Tablets} \times 100]$ at each time point of test will be tabulated.

10.5.2 Factors that May Affect the Efficacy

Office blood pressure will be tabulated by patient background factors (e.g., sex, age) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of other antihypertensive).

11.0 Posting of Survey Information

Takeda Pharmaceutical Company Limited will post survey information on Clinical Trials.gov and an open website (JAPIC-CTI*) before starting the survey.

* Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organization

12.1 Administrative Manager

PPD

Company Limited

Takeda Pharmaceutical

12.2 Central Registration Center

PPD

13.0 Contract Research Organization

PPD



14.0 Other Necessary Matters

14.1 Revision of the Protocol

During the survey, attention will be paid to comprehend the status of progression of the survey, presence or absence of unexpected adverse drug reactions (ADRs)/serious ADRs (based on precautions), presence or absence of increased incidence of certain ADRs, and appropriateness of survey items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the survey, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

14.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix Observation schedule

Time point of survey Survey item		Observation period															
		At patient registration	Start of treatment	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment	After 4 months of treatment	After 5 months of treatment	After 6 months of treatment	After 7 months of treatment	After 8 months of treatment	After 9 months of treatment	After 10 months of treatment	After 11 months of treatment	After 12 months of treatment	At discontinuation of treatment	
Patient registration	Date of prescription of Zacras Combination Tablets	○															
	Patient identification number	○															
	Patient initials	○															
	Sex	○															
	Date of birth	○															
	Inclusion/exclusion criteria	○															
	Presence or absence of breast-feeding (only females)	○															
Patient demographics and baseline characteristics	Time of diagnosis of hypertension		○														
	Diagnostic category		○														
	Predisposition to hypersensitivity		○														
	Concurrent illness		○														
	Medical history		○														
	Height, body weight		○														
	Smoking history		○														
	Drinking history		○														
	Presence or absence of breast-feeding (only females)		○														
Treatment given, etc.	Details on the use of Zacras Combination Tablets		← ○ →														○
	Details on the use of other antihypertensive		← ○ →														○
	Details on the use of concomitant non-antihypertensive drug		← ○ →														○
Tests/observations, etc.	Office blood pressure		○	○	○	○	○	○	○	○	○	○	○	○	○	○	
	Pulse rate		○	○	○	○	○	○	○	○	○	○	○	○	○	○	
	White blood cell count		← ○ →														○
	Platelet count		← ○ →														○
	AST		← ○ →														○
	ALT		← ○ →														○

	γ -GTP		←—————○—————→	○
	Serum creatinine		←—————○—————→	○
	BUN		←—————○—————→	○
	Serum potassium		←—————○—————→	○
	Presence or absence of pregnancy (only females)		←—————○—————→	○
	Adverse event		←—————○—————→	○

○ : Performed

← ○ → Performed throughout the period

Protocol for Specified Drug-Use Survey
Specified Drug-Use Survey (“Long-Term Use Survey”)
on Zacras Combination Tablets LD & HD

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Sponsor	Takeda Pharmaceutical Company Limited

Table of Contents

1.0	Background	4
2.0	Objectives.....	4
3.0	Planned Sample Size and Rationale	4
3.1	Planned Sample Size	4
3.2	Rationale.....	4
4.0	Survey Population	5
4.1	Exclusion Criteria.....	5
5.0	Dosage and Administration	5
6.0	Planned Number of Medical Institutions by Department.....	6
7.0	Methods.....	6
7.1	Observation Period.....	6
7.2	Request to and Contract with the Study Site	6
7.3	Method of Patient Registration.....	6
7.4	Completion and Submission of Case Report Form	7
7.5	Actions to be Taken in Case of Serious Adverse Events	7
8.0	Planned Period.....	7
9.0	Survey Items.....	7
9.1	Entries into the Patient Registration Form	7
9.2	Entries into the Case Report Form	8
9.2.1	Cover of the Case Report Form.....	8
9.2.2	Patient Demographics and Baseline Characteristics	8
9.2.3	Treatment Given.....	8
9.2.4	Tests/Observations.....	8
9.2.4.1	Vital Signs	8
9.2.4.2	Laboratory Tests	9
9.2.4.3	Other Observations.....	9
9.2.5	Adverse Events (AEs)	9
10.0	Analysis Items and Methods	11
10.1	Matters on Patient Composition	11
10.2	Patient Demographics and Baseline Characteristics	11
10.3	Treatment Given.....	11
10.4	Matters on Safety	11
10.4.1	Occurrence of Adverse Events	12
10.4.2	Factors that May Affect the Safety.....	12
10.5	Matters on Efficacy	12
10.5.1	Office Blood Pressure.....	12
10.5.2	Factors that May Affect the Efficacy.....	12
11.0	Posting of Survey Information	12
12.0	Organization	12

12.1	Administrative Manager.....	12
12.2	Central Registration Center.....	12
13.0	Contract Research Organization.....	13
14.0	Other Necessary Matters	13
14.1	Revision of the Protocol.....	13
14.2	Actions to be Taken for Problems and Questions.....	13
Appendix Observation schedule.....		14

1.0 Background

Since drugs for hypertension are generally used for a long period of time, the safety of long-term use must be established. While the safety of long-term use of Zacras Combination Tablets LD & HD (hereinafter referred to as Zacras Combination Tablets) was already evaluated in a Japanese Phase III long-term clinical study (duration of treatment: 52 weeks, number of evaluated subjects: 368), it is necessary to evaluate the safety in more patients in clinical settings after marketing, a population that, unlike the study population, receive the drug in diverse situations.

Accordingly, a specified drug-use survey (hereinafter referred to as the survey) is planned to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice. This survey will be conducted in compliance with Good Post-marketing Study Practice (GPSP) ordinance and related requirements.

2.0 Objectives

To evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in hypertensive patients in daily medical practice

3.0 Planned Sample Size and Rationale

3.1 Planned Sample Size

1,000 patients

3.2 Rationale

Patient populations identified as important missing information from Japanese clinical studies of Zacras Combination Tablets are patients with renal impairment, patients with hepatic impairment, and elderly patients (≥ 75 years old). The sample size required to evaluate the safety and efficacy of long-term use of Zacras Combination Tablets in these patient populations was calculated by reference to previous results. More specifically, according to final tabulation (number of patients included in safety evaluation: 3,300) in a previous specified drug-use survey (long-term use survey in hypertension) of a fixed-dose combination (UNISIA Combination Tablets) of an angiotensin receptor blocker (ARB) (candesartan) and a Ca antagonist (amlodipine), which belongs to the pharmacologically same class as Zacras Combination Tablets, patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 6.9%, 11.5%, and 65.2% (36.8%) of all patients, respectively. According to final tabulation (number of patients included in safety evaluation: 4,152) in a drug use-results survey of candesartan alone (BLOPRESS Tablets), patients with renal impairment, patients with hepatic impairment, and elderly patients (and those ≥ 75 years old) accounted for 9.5%, 10.6%, and 53.2% (22.1%), respectively. With a target sample size of 1,000 patients for the present survey, 70 patients with renal impairment, 100 patients with hepatic impairment, and 500 elderly patients (and 200 patients ≥ 75 years old)

are expected to be collected, probably allowing the safety and efficacy evaluation in these populations. This calculation is not based on statistical estimation.

4.0 Survey Population

The survey population consists of hypertensive patients who do not meet any of the exclusion criteria listed in Section 4.1. Refer to the “Precautions for Indication” (presented below) and “Precautions” sections in the package insert.

<Precautions for Indication>

Zacras Combination Tablets should not be used as the first-line treatment of hypertension. An excessive drop in blood pressure may occur.

4.1 Exclusion Criteria

Patients who meet any of the following criteria should be excluded from the survey:

- (1) Patients with a history of hypersensitivity to any of the ingredients of Zacras Combination Tablets or other dihydropyridines
- (2) Patients who are or may be pregnant
- (3) Diabetic patients taking aliskiren fumarate (excluding those with markedly poor blood pressure control despite other antihypertensive treatments)

5.0 Dosage and Administration

For adults, one Zacras Combination Tablet (20 mg/2.5 mg or 20 mg/5 mg of azilsartan/amlodipine) will be administered orally once daily. Zacras Combination Tablets should not be used as the first-line treatment of hypertension. Refer to the “Precautions for Dosage and Administration” (presented below) and “Precautions” sections in the package insert.

<Precautions for Dosage and Administration>

- (1) It should be determined whether Zacras Combination Tablets are indicated for each patient individually based on the following Dosage and Administration and Precautions for Dosage and Administration of azilsartan and amlodipine besilate, as well as other relevant information:

Azilsartan

Dosage and Administration

For adults, azilsartan 20 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on age and symptoms, with the maximum daily dose being 40 mg.

Precautions for Dosage and Administration

It should be carefully determined whether or not azilsartan is indicated while keeping the hypotensive effect of azilsartan in mind. Initiation of treatment at a low dose below 20 mg should also be considered.

Amlodipine besilate

•Hypertension

Dosage and Administration

For adults, amlodipine 2.5 to 5 mg should usually be administered orally once daily. The dose may be increased or reduced as appropriate based on symptoms. In the case of insufficient response, the dose may be increased up to 10 mg given once daily.

(2) As a general rule, switching to Zacras Combination Tablets should be considered for patients receiving azilsartan 20 mg with amlodipine 2.5 to 5 mg or patients with poor blood pressure control despite treatment with either one of these treatments.

6.0 Planned Number of Medical Institutions by Department

Internal medicine and other departments	Approximately 250 medical institutions
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7.0 Methods

7.1 Observation Period

12 months

7.2 Request to and Contract with the Study Site

Request and contract for participation in the survey will be made using a paper case report form (CRF). A medical representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda's MR) will explain the objectives, contents, and methods of the survey to the investigator based on "Request for cooperation for specified drug-use survey," "Implementation outline," "Patient registration form (sample)," and "Case report form (sample)" to enter into a written contract with the study site and request the study site to conduct a survey within a specified period.

7.3 Method of Patient Registration

Patients will be registered using the central registration system via fax. After the start of the contract with the study site, the investigator shall register each patient for whom Zacras Combination Tablets are prescribed by faxing a patient registration form containing patient registration information (refer to Section 9.1) to the central registration center (refer to Section 12.2) within 14 days after prescription of Zacras Combination Tablets (day of prescription designated as day 0 and day following the day of prescription designated as 1 day after prescription). No patient can be registered before Zacras Combination Tablets are actually prescribed. Patients determined by the central registration center to be ineligible for any reason cannot be registered. The investigator shall register a new patient using a new patient registration form supplied by Takeda's MR.

Takeda's MR will supply a CRF, which will be issued after the central registration center

decides to register the relevant patient, to the investigator.

7.4 Completion and Submission of Case Report Form

For each of all registered patients, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of the observation period. Any failure to confirm the intake of Zacras Combination Tablets shall be specified (no further information is required).

For patients discontinued from treatment with Zacras Combination Tablets for any reason during the observation period, the investigator shall complete and submit a CRF to Takeda's MR within approximately 1 month after the end of required observation. For any patient discontinued from treatment with Zacras Combination Tablets due to an adverse event, the investigator shall complete and submit a CRF to Takeda's MR after monitoring the patient as long after discontinuation of treatment as possible until the adverse event is confirmed to have resolved or be resolving.

7.5 Actions to be Taken in Case of Serious Adverse Events

The investigator shall immediately communicate any serious adverse event in the observation period to Takeda's MR. In addition, the investigator shall provide detailed information at the request of Takeda's MR.

8.0 Planned Period

Survey period: From June 2014 to 31 January 2017

Patient enrollment period: From June 2014 to 31 January 2016^{Note)}

^{Note)} Patient registration (receipt of a patient registration form via fax) will not be accepted on 1 February 2016 onwards even if Zacras Combination Tablets are prescribed by 31 January 2016.

If the number of patients enrolled in the survey reaches the planned sample size before 31 January 2016, acceptance of registration will be terminated before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will be changed accordingly.

9.0 Survey Items

The investigator shall enter the items listed below into the patient registration form and the CRF. The survey schedule is presented in Appendix.

9.1 Entries into the Patient Registration Form

1) Survey items

Name of the medical institution, name of a physician who completes the patient registration form, date of prescription of Zacras Combination Tablets, patient identification number, patient initials, sex, date of birth, assessment based on the inclusion criteria, assessment

based on the exclusion criteria, presence or absence of breast-feeding (only females)

2) Time points of survey

At patient registration

9.2 Entries into the Case Report Form

9.2.1 Cover of the Case Report Form

Date of final entry into the CRF, name of a physician who completes the CRF

9.2.2 Patient Demographics and Baseline Characteristics

1) Survey items

Time of diagnosis of hypertension, diagnostic category (at the start of treatment with Zacras Combination Tablets), predisposition to hypersensitivity (presence or absence and details), concurrent illness (presence or absence and details), medical history (presence or absence and details), height, body weight, smoking history, drinking history, presence or absence of breast-feeding (at the start of treatment with Zacras Combination Tablets) [only females]

2) Time points of survey

At the start of treatment with Zacras Combination Tablets

9.2.3 Treatment Given

1) Survey items

Details on the use of Zacras Combination Tablets (daily dose, duration of treatment, and reason for discontinuation of treatment), details on the use of other antihypertensive* (presence or absence, name of the drug, daily dose, and duration of treatment), details on the use of concomitant non-antihypertensive drug (presence or absence, name of the drug, and purpose of use)

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

* Period from 2 months before the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment) for details on the use of other antihypertensive

9.2.4 Tests/Observations

9.2.4.1 Vital Signs

1) Tests/observations

Office blood pressure (systolic/diastolic), pulse rate

2) Time points of survey

Time points of measurement at the start of treatment with Zacras Combination Tablets and after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 months of treatment (or discontinuation of

treatment)

9.2.4.2 Laboratory Tests

1) Test parameters

White blood cell count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), serum creatinine, blood urea nitrogen (BUN), serum potassium

2) Time points of survey

Time points of test from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.4.3 Other Observations

1) Observations

Presence or absence of pregnancy in the observation period (only females)

If pregnancy is detected during the observation period, treatment with Zacras Combination Tablets should be discontinued immediately, and Takeda's MR should be informed. The investigator shall provide detailed information (including information up to delivery such as premature delivery, wherever possible) using a pregnancy sheet at the request of Takeda's MR.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of treatment (or discontinuation of treatment)

9.2.5 Adverse Events (AEs)

1) Survey items

Presence or absence of AE (refer to Table 1), AE term, date of onset, seriousness and reason for seriousness (refer to Table 2), presence or absence of discontinuation of treatment with Zacras Combination Tablets, date of outcome assessment, outcome, causal relationship to Zacras Combination Tablets* (refer to Table 3)

Patients with "not resolved" or "unknown" outcome or "unevaluable" causal relationship should be followed up wherever possible.

* For the causal relationship to Zacras Combination Tablets, the rationale for "not related" and the reason for "unevaluable" shall be collected.

Note) Additional points to consider for AEs

Abnormal worsening of target disease, for instance, worsening beyond the expected natural course of the disease, will be handled as an AE, but expected worsening of target disease should not be handled as an AE.

2) Time points of survey

Period from the start of treatment with Zacras Combination Tablets to 12 months of

treatment (or discontinuation of treatment)

Table 1 Definition of adverse events

<p>An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable or unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.</p> <p>The following are also handled as AEs:</p> <ul style="list-style-type: none"> •Symptoms and so forth that occur in infants breast-fed by their mothers under treatment with a drug •Symptoms and so forth that occur in children treated with a drug •Symptoms and so forth that occur as a result of occupational exposure to a drug •Symptoms and so forth that occur after administration of counterfeit medicines of our ethical drugs
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Table 2 Criteria for assessing seriousness

An AE satisfying any of the following is assessed as serious:

1. Results in death (death)
2. Is life-threatening (risk of death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Leads to a congenital anomaly/birth defect (congenital anomaly)
6. Is an important medical event according to 1 to 5 described above, including AEs in Takeda Medically Significant AE List

Takeda Medically Significant AE List

•Acute respiratory failure/acute respiratory distress syndrome (ARDS)	•Anaphylactic shock
•Torsade de pointes / ventricular fibrillation / ventricular tachycardia	•Acute renal failure
•Malignant hypertension	•Pulmonary hypertension
•Convulsive seizures (including convulsion and epilepsy)	•Pulmonary fibrosis (including interstitial pneumonia)
•Agranulocytosis	•Neuroleptic malignant syndrome / malignant hyperthermia
•Aplastic anemia	•Spontaneous abortion / stillbirth and fetal death
•Toxic epidermal necrolysis / oculomucocutaneous syndrome (Stevens-Johnson syndrome)	•Confirmed or suspected transmission of infectious agent by a medicinal product
•Hepatic necrosis	•Confirmed or suspected endotoxin shock
•Acute liver failure	

Table 3 Criteria for assessing the relationship of each adverse event to Zacras Combination Tablets

Assessment	Criteria for assessment
Related	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, may also be responsible
Not related	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments
Unevaluable	Information necessary for evaluation, including temporal sequence from administration of a drug (including the course after withdrawal of the drug), underlying diseases, concurrent illnesses, concomitant drugs, and concomitant treatments, is not sufficient.

10.0 Analysis Items and Methods

10.1 Matters on Patient Composition

The number of enrolled patients, number of patients from whom the CRF is collected, number of patients included in safety/efficacy analysis, number of patients excluded from analysis, and reason for exclusion will be tabulated.

10.2 Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics, including sex, age, duration of disease, predisposition to hypersensitivity, and concurrent illness, will be tabulated.

10.3 Treatment Given

Details on the use of Zacras Combination Tablets, details on the use of other antihypertensive, and details on the use of concomitant non-antihypertensive drug will be tabulated.

10.4 Matters on Safety

For the safety analysis set, data will be tabulated as described below. AEs will be coded according to the MedDRA/J and summarized using preferred term (PT) and system organ class (SOC).

10.4.1 Occurrence of Adverse Events

For AEs reported during the observation period, the incidence will be tabulated by type, time of onset, seriousness, and causal relationship to Zacras Combination Tablets.

10.4.2 Factors that May Affect the Safety

For AEs reported during the observation period, the incidence will be tabulated by patient background factors (e.g., sex, age, presence or absence of concurrent renal impairment, presence or absence of concurrent hepatic impairment) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of concomitant drug).

10.5 Matters on Efficacy

For the efficacy analysis set, data will be tabulated as described below.

10.5.1 Office Blood Pressure

For office blood pressure, measured value, change (measured value at each post-baseline time point of measurement - measured value at the start of treatment with Zacras Combination Tablets), and percentage change $[(\text{measured value at each time point of measurement} - \text{measured value at the start of treatment with Zacras Combination Tablets}) \div \text{measured value at the start of treatment with Zacras Combination Tablets} \times 100]$ at each time point of test will be tabulated.

10.5.2 Factors that May Affect the Efficacy

Office blood pressure will be tabulated by patient background factors (e.g., sex, age) and treatment given (e.g., details on the use of Zacras Combination Tablets, details on the use of other antihypertensive).

11.0 Posting of Survey Information

Takeda Pharmaceutical Company Limited will post survey information on Clinical Trials.gov and an open website (JAPIC-CTI^{*}) before starting the survey.

^{*} Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organization

12.1 Administrative Manager

PPD

Company Limited

Takeda Pharmaceutical

12.2 Central Registration Center

PPD

13.0 Contract Research Organization

PPD



14.0 Other Necessary Matters

14.1 Revision of the Protocol

During the survey, attention will be paid to comprehend the status of progression of the survey, presence or absence of unexpected adverse drug reactions (ADRs)/serious ADRs (based on precautions), presence or absence of increased incidence of certain ADRs, and appropriateness of survey items, and this protocol will be reviewed and revised if necessary. If partial change to dosage and administration or indications is approved during the survey, the necessity of revising the protocol will be discussed if necessary, and the protocol will be revised as needed.

14.2 Actions to be Taken for Problems and Questions

If any safety or efficacy problem is detected, data will be carefully examined to discuss measures.

Appendix Observation schedule

Time point of survey Survey item		Observation period															
		At patient registration	Start of treatment	After 1 month of treatment	After 2 months of treatment	After 3 months of treatment	After 4 months of treatment	After 5 months of treatment	After 6 months of treatment	After 7 months of treatment	After 8 months of treatment	After 9 months of treatment	After 10 months of treatment	After 11 months of treatment	After 12 months of treatment	At discontinuation of treatment	
Patient registration	Date of prescription of Zacras Combination Tablets	○															
	Patient identification number	○															
	Patient initials	○															
	Sex	○															
	Date of birth	○															
	Inclusion/exclusion criteria	○															
	Presence or absence of breast-feeding (only females)	○															
Patient demographics and baseline characteristics	Time of diagnosis of hypertension		○														
	Diagnostic category		○														
	Predisposition to hypersensitivity		○														
	Concurrent illness		○														
	Medical history		○														
	Height, body weight		○														
	Smoking history		○														
	Drinking history		○														
	Presence or absence of breast-feeding (only females)		○														
Treatment given, etc.	Details on the use of Zacras Combination Tablets		← ○ →														○
	Details on the use of other antihypertensive		← ○ →														○
	Details on the use of concomitant non-antihypertensive drug		← ○ →														○
Tests/observations, etc.	Office blood pressure		○	○	○	○	○	○	○	○	○	○	○	○	○	○	
	Pulse rate		○	○	○	○	○	○	○	○	○	○	○	○	○	○	
	White blood cell count		← ○ →														○
	Platelet count		← ○ →														○
	AST		← ○ →														○
	ALT		← ○ →														○

	γ -GTP		←	○	→	○
	Serum creatinine		←	○	→	○
	BUN		←	○	→	○
	Serum potassium		←	○	→	○
	Presence or absence of pregnancy (only females)		←	○	→	○
	Adverse event		←	○	→	○

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← ○ → : Performed throughout the period