



Title: Takecab Tablets Special Drug Use Surveillance “Suppression of gastric or duodenal ulcer recurrence on non-steroidal anti-inflammatory drugs: Long-term use”

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

Special Drug Use Surveillance Protocol

Takecab Tablets Special Drug Use Surveillance

“Suppression of gastric or duodenal ulcer recurrence on non-steroidal anti-inflammatory drugs: Long-term use”

Sponsor Takeda Pharmaceutical Company Limited
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1.0 Background

Administration of Takecab Tablets for suppression of gastric or duodenal ulcer recurrence on non-steroidal anti-inflammatory drugs (NSAIDs) is anticipated to be continued long-term in routine clinical settings. Administration of Takecab Tablets 10 mg for suppression of gastric or duodenal ulcer recurrence on NSAIDs was evaluated for 24 weeks (168 days) or more in 166 patients and 48 weeks (336 days) or more in 137 patients in a Japanese phase III double-blind comparative study and long-term extension, and raised no particular safety issues. To verify the safety of Takecab Tablets used in routine clinical practice and the consistency of the long-term safety profile with the known safety profile of the drug, the present special drug use surveillance has been planned.

This surveillance will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and relevant regulatory requirements.

2.0 Objectives

To evaluate the safety and efficacy of Takecab Tablets for up to 12 months in patients on NSAIDs in routine clinical practice

3.0 Planned sample size and rationale

3.1 Planned sample size

1,000 patients

3.2 Rationale

The target sample size is set to 1000 for collection of 12-month therapy data from 300 patients. Based on the results from Takepron (lansoprazole) post-marketing surveillance*, the percentage of patients given 12-month therapy is conservatively assumed to be 30%. Thus, a target sample size of 1000 would allow collection of 12-month therapy data from 300 patients.

With the data collection from 300 patients, an adverse drug reaction (ADR) occurring with an incidence of 1% or more can be detected with a probability of at least 95%, which should allow determination of ADRs characteristic of long-term use of the drug.

*“Reflux esophagitis/maintenance therapy 3 to 6 months”: 6-month therapy in 57%

“Suppression of ulcer recurrence on low-dose aspirin: Long-term use”: 12-month therapy in 79.1%

“Suppression of ulcer recurrence on NSAIDs: Long-term use”: 12-month therapy in 46.1%

4.0 Surveillance population

This surveillance will enroll patients who are on NSAIDs (except low-dose aspirin) for control of pain of rheumatoid arthritis, osteoarthritis, and other diseases (including those who start Takecab therapy on the same day as the day of initiation of NSAIDs) and who meet the additional inclusion criterion and do not meet the exclusion criteria specified below. The PRECAUTIONS section of the Takecab package insert should also be referenced in the

enrollment judgment.

4.1 Inclusion criterion

Patients who are receiving NSAIDs (excluding low-dose aspirin) for pain control for rheumatoid arthritis, osteoarthritis, etc. (including patients who start Takecab therapy on the same day of initiation of NSAID) and also meet the following criteria will be included:

Patients with a history of gastric or duodenal ulcer

Refer to Precautions in the package insert.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded:

- (1) Patients with gastric or duodenal ulcer at initiation of Takecab therapy
- (2) Patients with active upper gastrointestinal haemorrhage at initiation of Takecab therapy
- (3) Patients with a history of hypersensitivity to any ingredients of Takecab Tablets
- (4) Patients receiving atazanavir sulfate or rilpivirine hydrochloride

5.0 Dosage and administration

The usual adult dosage is 10 mg of vonoprazan administered orally once daily. The PRECAUTIONS section of the Takecab package insert should also be referenced.

6.0 Planned number of surveillance sites by specialty department

Approximately 300 sites, including the rheumatology and orthopedic surgery departments

7.0 Methods

7.1 Duration of observation

12 months

This surveillance will be ended when either criterion (1) or (2) specified below is found to be met.

- (1) If Takecab therapy is discontinued
- (2) If NSAIDS are discontinued

If either a gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion develops during combination therapy with Takecab Tablets and NSAIDs, observation will be continued up to assessment of the post-treatment outcome of the ulcer/lesion and the surveillance will then be ended.

7.2 Request to and contract with medical institutions

The surveillance implementation will use a Web-based electronic data capture system (CC1 [REDACTED]). Upon request, a representative of Takeda Pharmaceutical Company Limited. (hereinafter referred to as "Takeda representative") will explain to the potential surveillance investigator about the surveillance objectives and contents, as well as how to use CC1 [REDACTED] and enter the electronic signature and handling of the user ID and the password according to the

“Request for Cooperation with Special Drug Use Surveillance,” “Surveillance Implementation Outline,” “**CCI** [REDACTED] Data Entry screen images” and “**CCI** [REDACTED] User Manual (brief version).” If the request is accepted, a written contract for the surveillance within the specified period will be made with the medical institution.

7.3 Patient enrollment method

Patients will be enrolled using a centralized enrollment method via **CCI** [REDACTED]. For patients prescribed Takecab Tablets on or after the first day of the contract period for the medical institution, the surveillance investigators will enter the patient information required for enrollment (see Section 9.1) and the electronic signature in **CCI** [REDACTED] within 14 days after the prescription of Takecab Tablets (with the day of prescription counted as zero and the day following prescription counted as “1 day after prescription”).

7.4 Data entry to the survey form (electronic) and electronic signature

The surveillance investigator or the persons designated by the surveillance investigator* will enter data on patient demographics, treatment details, etc. for all the enrolled patients in **CCI** [REDACTED], and the surveillance investigator will provide the electronic signature, roughly within 1 month after the end of required observations at Month 12 of Takecab therapy. If administration of this drug could not be confirmed, this fact should be entered (no other data are required).

For patients who discontinued treatment with Takecab Tablets for certain reasons during the observation period, the surveillance investigator or the persons designated by the surveillance investigator will enter data on patient demographics, treatment details, etc. in **CCI** [REDACTED], and the surveillance investigator will provide the electronic signature roughly within 1 month after the end of required observations. However, for patients who discontinued Takecab therapy because of onset of an adverse event (AE), even after the discontinuation of this drug, the surveillance investigator will continue observation as far as possible up to resolution or improvement of the adverse event. The surveillance investigator or the persons designated by the surveillance investigator will then enter the observation result in **CCI** [REDACTED], and the surveillance investigator will provide the electronic signature.

*The persons designated by the surveillance investigator should be persons who belong to the surveillance site (including persons with a service contract with the surveillance site such as a dispatched clinical research coordinator). The physician responsible for implementation of the surveillance (1 each from the surveillance sites or treating departments, determined at the time of diagnosis) will prepare the records of designation and the date of designation (any format allowed) and submit them with his/her signature or printed name and seal to the Takeda representative before the persons designated by the surveillance investigator enter data in **CCI** [REDACTED].

7.5 Actions taken for serious adverse events

If any serious AE occurs during the observation period, the surveillance investigator will immediately report it to a Takeda representative. If requested by the Takeda representative, the surveillance investigator will provide detailed information separately.

8.0 Planned surveillance period

Surveillance period: September 2016 to April 30, 2020

Patient enrollment period: September 2016 to April 30, 2019 ^{Note)}

^{Note)} No patient enrollment (via **CCI** [REDACTED]) will be acceptable on or after May 1, 2019, even if Takecab is prescribed by April 30, 2019.

If the total number of the enrolled patients in the entire surveillance reach the planned sample size before April 30, 2019, patient enrollment will be closed before the end of the patient enrollment period. If the patient enrollment period is shortened, the surveillance period will also be changed according to the shortened enrollment period.

9.0 Surveillance items

The surveillance investigator or the persons designated by the surveillance investigator will enter data of the following items into **CCI** [REDACTED]. The surveillance schedule is shown in the Appendix.

9.1 Patient enrollment

1) Surveillance items

Date of prescription of Takecab Tablets, patient identification number, patient initials, sex, date of birth, assessment against the inclusion criteria (details of the history of gastric or duodenal ulcer (time and site of onset)), assessment against the exclusion criteria

2) Time of data collection

At enrollment of the patient

9.2 Patient demographics information

1) Surveillance items

Reason for use of NSAIDs, time of initiation of NSAIDs, inpatient/outpatient classification (at initiation of Takecab therapy), hypersensitive diathesis (presence or absence, and details), complication (excluding the reason for use of NSAIDs: presence or absence, and details), height, weight, presence or absence of *Helicobacter pylori* infection (at initiation of Takecab therapy), smoking history, drinking history, presence or absence of stress as a risk factor of onset of gastric or duodenal ulcer, detailed use of acid secretion inhibitors for suppression of gastric or duodenal ulcer recurrence within 1 month before initiation of Takecab therapy (presence or absence, and name of drug)

2) Time of data collection

At initiation of Takecab therapy

9.3 Treatment information

1) Surveillance items

Takecab therapy details (daily dose, therapy dates, and reason for discontinuation), NSAID therapy details (name of drug, daily dose, and therapy dates), reason for use of Takecab after the end of NSAID therapy, concomitant drug (other than NSAIDs) details (presence or absence, name of drug, and reason for use)

2) Time of data collection

From initiation of Takecab therapy to Month 12 (or discontinuation of the therapy)

9.4 Tests and observations

9.4.1 Gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion after initiation of Takecab therapy

1) Data items

Gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion (presence or absence of onset, details, basis for the diagnosis, and date of endoscopy or diagnosis)

2) Time of data collection

From initiation of Takecab therapy to Month 12 (or discontinuation of the therapy)

9.4.2 Liver function tests

1) Test parameters

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ -GTP), alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH)

2) Time of data collection

At the testing from initiation of Takecab therapy* to Month 12 (or discontinuation of the therapy)

*Within 1 month before initiation of Takecab therapy

9.4.3 Serum gastrin

1) Test parameter

Serum gastrin level

2) Time of data collection

At the testing from initiation of Takecab therapy* to Month 12 (or discontinuation of the therapy)

*Within 1 month before initiation of Takecab therapy

9.4.4 Other items of observations

1) Observation items

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

Any pregnancy found during the observation period should be immediately notified to a

Takeda representative. Based on a request by a Takeda representative, the surveillance investigator will provide detailed information (wherever possible up to the outcome of pregnancy, such as premature delivery) separately using a pregnancy report form.

2) Time of data collection

From initiation of Takecab therapy to Month 12 (or discontinuation of the therapy)

9.5 Adverse events

1) Surveillance items

Presence or absence of AEs (see Table 1), AE term, date of onset, seriousness and reason for the assessment as serious (see Table 2), reason for discontinuation of Takecab, outcome assessment date, outcome, causal relationship to Takecab* (see Table 3) If the outcome is “not resolved” or “unknown,” or if the causal relationship is “unassessable,” the event should be followed as far as possible.

Detailed event information (clinical course, results of diagnostic tests, etc.) should be collected as much as possible in the event of hepatic function disorder, fracture, gastrointestinal infection with *Clostridium difficile*, or neuroendocrine tumor.

*If the causal relationship to Takecab is “Not related,” the basis for the assessment should be recorded. If the causal relationship to Takecab is “Unassessable,” the reason should be recorded.

Note) Special guidance about reporting of AEs:

Onset of a gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion, which is an efficacy endpoint, is not regarded as an AE.

Serum gastrin can increase due to the pharmacological action of Takecab. However, if Takecab therapy is discontinued because of increased serum gastrin, this event should be handled as an AE.

2) Time of data collection

From initiation of Takecab therapy to Month 12 (or discontinuation of the therapy)

Table 1 Definition of an Adverse Event

<p>An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.</p> <p>Note that the following events will also be handled as adverse events:</p> <ul style="list-style-type: none">• Any manifestation in an infant breastfed by a mother taking this drug• Any untoward manifestation in a child given this drug• Any manifestation due to occupational exposure to this drug• Any manifestation due to a counterfeit product of a prescription drug marketed by Takeda• Any untoward manifestation in a patient given this drug revealed by a lawsuit or any other legal action
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Table 2 Criteria for Serious Adverse Events

<p>An adverse event is assessed as “serious” if it results in any of the following outcomes:</p> <ol style="list-style-type: none">1. results in death (Death),2. is life-threatening (Life-threatening),3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization),4. results in persistent or significant disability/incapacity (Disability),5. leads to a congenital anomaly or birth defect (Congenital anomaly), or6. is any other important medical event that does not fulfil 1 to 5 above. <p>Serious adverse events include events described in the “Takeda Medically Significant AE List.”</p> <p><u>Takeda Medically Significant AE List</u></p> <table><tbody><tr><td>- Acute respiratory failure / Acute respiratory distress syndrome (ARDS)</td><td>- Anaphylactic shock</td></tr><tr><td>- Torsade de pointes / Ventricular fibrillation / Ventricular tachycardia</td><td>- Acute renal failure</td></tr><tr><td>- Malignant hypertension</td><td>- Pulmonary hypertension</td></tr><tr><td>- Convulsive seizure (including convulsion and epilepsy)</td><td>- Pulmonary fibrosis (including interstitial pneumonia)</td></tr><tr><td>- Agranulocytosis</td><td>- Neuroleptic malignant syndrome/ Malignant hyperthermia</td></tr><tr><td>- Aplastic anaemia</td><td>- Spontaneous abortion / Stillbirth and fetal death</td></tr><tr><td>- Toxic epidermal necrolysis / Oculomucocutaneous syndrome (Stevens-Johnson syndrome)</td><td>- Confirmed or suspected transmission of infectious agent by a medicinal product</td></tr><tr><td>- Hepatic necrosis</td><td>- Confirmed or suspected endotoxin shock</td></tr><tr><td></td><td>- Acute hepatic failure</td></tr></tbody></table>	- 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 seizure (including convulsion and epilepsy)	- Pulmonary fibrosis (including interstitial pneumonia)	- Agranulocytosis	- Neuroleptic malignant syndrome/ Malignant hyperthermia	- Aplastic anaemia	- 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 hepatic failure	
- Acute respiratory failure / Acute respiratory distress syndrome (ARDS)	- Anaphylactic shock																		
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- Convulsive seizure (including convulsion and epilepsy)	- Pulmonary fibrosis (including interstitial pneumonia)																		
- Agranulocytosis	- Neuroleptic malignant syndrome/ Malignant hyperthermia																		
- Aplastic anaemia	- 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 hepatic failure																		

Table 3 Assessment of the causal relationship between an adverse event and Takecab

Causality classification	Definition
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which possible involvement of this drug can be considered, although factors other than this drug, such as the primary disease, complication, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can reasonably be explained by other factors, such as the primary disease, complication, concomitant drugs or concurrent treatments.
Unassessable	The causality cannot be assessed because of insufficiency of required information, such as temporal sequence of the event onset relative to administration of this drug (including the course after withdrawal of the drug), primary disease, complication, concomitant drugs, and concurrent treatments.

10.0 Analysis items and methods

10.1 Disposition of patients

Number of patients enrolled, number of patients with collected survey forms (electronic), numbers of patients for safety and efficacy analyses, number of patients excluded from analysis, reasons for exclusion, etc. will be summarized.

10.2 Patient demographics

Patient demographic data such as sex, age, hypersensitive diathesis, and complication will be summarized.

10.3 Treatment details

Detailed use of Takecab, NSAIDs, and concomitant drugs (other than NSAIDs) will be summarized.

10.4 Safety data

The following data will be summarized using the safety analysis set. AEs will be coded using the MedDRA/J and summarized by Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Incidence of adverse events

AEs occurring during the observation period will be summarized using frequency count by event type, time of onset, seriousness, causal relationship to Takecab, etc.

10.4.2 Factors which may affect safety

ADRs occurring during the observation period will be summarized using frequency count,

with stratification of patients according to patient demographic factors (e.g., sex, age, reason for use of NSAIDs, any renal impairment, any hepatic impairment) and treatment details (e.g., detailed use of Takecab, detailed use of NSAIDs).

10.5 Efficacy data

The following data will be summarized using the efficacy analysis set.

10.5.1 Gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion after initiation of Takecab therapy

The presence or absence of onset of a gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion will be summarized.

10.5.2 Factors which may affect efficacy

The presence or absence of onset of a gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion will be summarized with stratification of patients according to patient demographic factors (e.g., sex, age, presence or absence of *Helicobacter pylori* infection) and treatment details (e.g., detailed use of Takecab, detailed use of NSAIDs).

11.0 Registration of surveillance information

Before initiation of the surveillance, Takeda Pharmaceutical Company Limited will register the surveillance information with an online public clinical trials registry:

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information
- National Institute of Health Clinical Trial Registration System: Clinical Trials.gov

12.0 Administrative structure

Responsible Manager

Post-marketing surveillance manager, Takeda Pharmaceutical Company Limited

13.0 Contract Research Organizations

(1) A2 Healthcare Corporation

Address: 1-4-1, Koishikawa, Bunkyo-ku, Tokyo

Duties: Data management and statistical analysis

(2) PRA Health Sciences K.K.

Address: 4-1-3, Kyutaromachi, Chuo-ku, Osaka-shi, Osaka

Duties: Data management, storage of records, PDF conversion of AE reports and supportive activities related to dissemination of information

(3) Fujitsu FIP Corporation

Address: 2-2-2, Nakanoshima, Kita-ku, Osaka-shi, Osaka

Duties: **CCI** construction and operation

14.0 Other necessary items

14.1 Protocol amendments

During the surveillance period, monitoring will be performed regarding the progress of the surveillance, occurrence of ADRs unexpected from the PRECAUTIONS and serious ADRs, any increase in the incidence of particular ADRs, validity of the surveillance items, etc., and the protocol will be reviewed and amended as necessary. If any partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the surveillance period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

14.2 Actions to be taken in response to detection of any issues or concerns

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix Observation schedule

Surveillance items	Time of data collection/entry	Observation period			
		At enrollment	Start of Takecab therapy	Month 12	Discontinuation of Takecab therapy
Patient enrollment	Date of prescription of Takecab Tablets	○			
	Patient identification number	○			
	Patient initials	○			
	Sex	○			
	Date of birth	○			
	Assessment against inclusion criterion (details of history of gastric or duodenal ulcer)	○			
	Assessment against exclusion criteria	○			
Patient demographics	Reason for use of NSAIDs			○	
	Time of initiation of NSAIDs			○	
	Inpatient/outpatient classification			○	
	Hypersensitive diathesis			○	
	Complication (excluding the reason for use of NSAIDs)			○	
	Height, weight			○	
	<i>H. pylori</i> infection			○	
	Smoking history			○	
	Drinking history			○	
	Presence or absence of stress as a risk factor of onset of gastric or duodenal ulcer			○	
	Detailed use of acid secretion inhibitors for suppression of gastric or duodenal ulcer recurrence within 1 month before initiation of Takecab therapy			○	
Treatment details	Detailed use of Takecab		←○→		○
	Detailed use of NSAIDs		←○→		○
	Reason for use of Takecab after the end of NSAID therapy		←○→		
	Detailed use of concomitant drugs (other than NSAIDs)		←○→		○
Assessments	Gastric/duodenal ulcer or gastric/duodenal haemorrhagic lesion after initiation of Takecab therapy		←○→		○
	Liver function tests		←○(Note)→		○
	Serum gastrin		←○(Note)→		○
	Pregnancy (women only)		←○→		○
	AE monitoring		←○→		○

○ : Performed

←○→ : Performed throughout the period

Note) From ≤1 month before initiation of Takecab therapy to Month 12