



Title: Drug Use Surveillance of Vonoprazan for "Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis"

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

Drug Use Surveillance Protocol

Drug Use Surveillance for Takecab Tablets

Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 7
Preparation date	April 3, 2018

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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI [REDACTED]). Prior to starting this surveillance, an officer of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda officer) will provide the

surveillance investigator with an explanation about the objective and contents of this surveillance, CCI operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “CCI Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on CCI will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreements with the study site, the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into CCI and will provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator or a person designated by the surveillance investigator* will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator or a person designated by the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, the surveillance investigator or a person designated by the surveillance investigator will enter the observation results into CCI and the surveillance investigator will provide an electronic signature.

*The person designated by the surveillance investigator will be a person belonging to the medical institution (including those who have contract agreements with a medical institution such as a contract research organization (CRO)). The physicians who are the surveillance directors (one will be appointed for each study site or its department at the time of conclusion of contract agreements) will prepare records of the designees and designation dates and (whatever the form is) provide a signature or a signature and a seal, and submit the records to a Takeda officer before the person designated by the surveillance investigator enters data into

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda officer. Upon request from a Takeda officer, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: March 2016 to October 31, 2018

Accrual period: March 2016 to August 31, 2018^{Note)}

^{Note)} Even for the patients with Takecab Tablets prescribed by August 31, 2018, patient enrollment (data entry in CCI) will not be accepted on and after September 1, 2018.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before August 31, 2018, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before August 31, 2018 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator or a person designated by the surveillance investigator will enter information on the items shown below into CCI. The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses (excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

*1: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

*2: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

*3: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*1})

*1: Mild: Occasionally or slightly symptomatic.

Moderate: Considerably symptomatic.

Severe: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance*².

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets*¹ to the end of the surveillance*²

*1: Within 1 month before the start of treatment.

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda officer. Upon request by the Takeda officer, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a

follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Unwanted symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company
- Unwanted symptoms that have developed in persons using the drug and have become known by a lawsuit or any other legal act

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”

1. Results in death (death)
2. Life-threatening (possible death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disorders)
5. Causes congenital anomalies
6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section

Takeda Medically Significant AE List

- | | |
|---|--|
| • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) | • Anaphylactic shock |
| • Torsades de pointes/ventricular fibrillation/ventricular tachycardia | • Acute renal failure |
| • Malignant hypertension | • Pulmonary hypertension |
| • Convulsive seizures (including convulsions and epilepsy) | • Pulmonary fibrosis (including interstitial pneumonia) |
| • Agranulocytosis | • Neuroleptic malignant syndrome/malignant hyperpyrexia |
| • Aplastic anemia | • Spontaneous abortions/stillbirths and fetal deaths |
| • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) | • Confirmed or suspected transmission of drug-mediated infection |
| • Acute hepatic failure | • Endotoxin shock or, suspected |
| • Hepatic necrosis | |

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance* will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited

PPD

13.0 Contract research organization

PPD

14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div>Surveillance information entry times</div> <div>Items for surveillance</div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		← <input type="radio"/> →					<input type="radio"/>
	Use of concomitant drugs		← <input type="radio"/> →					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		← <input type="radio"/> <small>Note 5)</small> →					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		← <input type="radio"/> →					<input type="radio"/>
	Adverse events		← <input type="radio"/> →					<input type="radio"/>

○ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, or at treatment discontinuation).

Note 5) Within 1 month before the start of treatment to the end of the surveillance.

Drug Use Surveillance Protocol

Drug Use Surveillance for Takecab Tablets

Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 6
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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI [REDACTED]). Prior to starting this surveillance, an officer of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda officer) will provide the

surveillance investigator with an explanation about the objective and contents of this surveillance, CCI operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “CCI Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on CCI will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreements with the study site, the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into CCI and will provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator or a person designated by the surveillance investigator* will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator or a person designated by the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, the surveillance investigator or a person designated by the surveillance investigator will enter the observation results into CCI and the surveillance investigator will provide an electronic signature.

*The person designated by the surveillance investigator will be a person belonging to the medical institution (including those who have contract agreements with a medical institution such as a contract research organization (CRO)). The physicians who are the surveillance directors (one will be appointed for each study site or its department at the time of conclusion of contract agreements) will prepare records of the designees and designation dates and (whatever the form is) provide a signature or a signature and a seal, and submit the records to a Takeda officer before the person designated by the surveillance investigator enters data into

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda officer. Upon request from a Takeda officer, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: March 2016 to October 31, 2018

Accrual period: March 2016 to August 31, 2018^{Note)}

Note) Even for the patients with Takecab Tablets prescribed by August 31, 2018, patient enrollment (data entry in CCI) will not be accepted on and after September 1, 2018.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before August 31, 2018, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before August 31, 2018 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator or a person designated by the surveillance investigator will enter information on the items shown below into CCI. The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses (excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

*1: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

*2: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

*3: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*1})

*1: Mild: Occasionally or slightly symptomatic.

Moderate: Considerably symptomatic.

Severe: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance*².

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets*¹ to the end of the surveillance*²

*1: Within 1 month before the start of treatment.

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda officer. Upon request by the Takeda officer, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a

follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Unwanted symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company
- Unwanted symptoms that have developed in persons using the drug and have become known by a lawsuit or any other legal act

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”

1. Results in death (death)
2. Life-threatening (possible death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disorders)
5. Causes congenital anomalies
6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section

Takeda Medically Significant AE List

- | | |
|---|--|
| • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) | • Anaphylactic shock |
| • Torsades de pointes/ventricular fibrillation/ventricular tachycardia | • Acute renal failure |
| • Malignant hypertension | • Pulmonary hypertension |
| • Convulsive seizures (including convulsions and epilepsy) | • Pulmonary fibrosis (including interstitial pneumonia) |
| • Agranulocytosis | • Neuroleptic malignant syndrome/malignant hyperpyrexia |
| • Aplastic anemia | • Spontaneous abortions/stillbirths and fetal deaths |
| • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) | • Confirmed or suspected transmission of drug-mediated infection |
| • Acute hepatic failure | • Endotoxin shock or, suspected |
| • Hepatic necrosis | |

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance* will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited

PPD



13.0 Contract research organization

PPD



14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div>Surveillance information entry times</div> <div>Items for surveillance</div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		◀────────○────────▶					<input type="radio"/>
	Use of concomitant drugs		◀────────○────────▶					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		◀────────○ <small>Note 5)</small> ────────▶					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		◀────────○────────▶					<input type="radio"/>
	Adverse events		◀────────○────────▶					<input type="radio"/>

○ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, or at treatment discontinuation).

Note 5) Within 1 month before the start of treatment to the end of the surveillance.

Drug Use Surveillance Protocol

Drug Use Surveillance for Takecab Tablets

Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 5
Preparation date	June 2, 2017

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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI [REDACTED]). Prior to starting this surveillance, an officer of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda officer) will provide the

surveillance investigator with an explanation about the objective and contents of this surveillance, CCI operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “CCI Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on CCI will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreements with the study site, the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into CCI and will provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator or a person designated by the surveillance investigator* will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator or a person designated by the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, the surveillance investigator or a person designated by the surveillance investigator will enter the observation results into CCI and the surveillance investigator will provide an electronic signature.

*The person designated by the surveillance investigator will be a person belonging to the medical institution (including those who have contract agreements with a medical institution such as a contract research organization (CRO)). The physicians who are the surveillance directors (one will be appointed for each study site or its department at the time of conclusion of contract agreements) will prepare records of the designees and designation dates and (whatever the form is) provide a signature or a signature and a seal, and submit the records to a Takeda officer before the person designated by the surveillance investigator enters data into

CCI

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda officer. Upon request from a Takeda officer, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: March 2016 to April 30, 2018

Accrual period: March 2016 to February 28, 2018^{Note)}

^{Note)} Even for the patients with Takecab Tablets prescribed by February 28, 2018, patient enrollment (data entry in CCI) will not be accepted on and after March 1, 2018.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before February 28, 2018, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before February 28, 2018 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator or a person designated by the surveillance investigator will enter information on the items shown below into CCI. The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses (excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

*1: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

*2: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

*3: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*1})

*1: Mild: Occasionally or slightly symptomatic.

Moderate: Considerably symptomatic.

Severe: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance*².

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets*¹ to the end of the surveillance*²

*1: Within 1 month before the start of treatment.

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda officer. Upon request by the Takeda officer, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a

follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Unwanted symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company
- Unwanted symptoms that have developed in persons using the drug and have become known by a lawsuit or any other legal act

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”

1. Results in death (death)
2. Life-threatening (possible death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disorders)
5. Causes congenital anomalies
6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section

Takeda Medically Significant AE List

- | | |
|---|--|
| • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) | • Anaphylactic shock |
| • Torsades de pointes/ventricular fibrillation/ventricular tachycardia | • Acute renal failure |
| • Malignant hypertension | • Pulmonary hypertension |
| • Convulsive seizures (including convulsions and epilepsy) | • Pulmonary fibrosis (including interstitial pneumonia) |
| • Agranulocytosis | • Neuroleptic malignant syndrome/malignant hyperpyrexia |
| • Aplastic anemia | • Spontaneous abortions/stillbirths and fetal deaths |
| • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) | • Confirmed or suspected transmission of drug-mediated infection |
| • Acute hepatic failure | • Endotoxin shock or, suspected |
| • Hepatic necrosis | |

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance* will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited

PPD



13.0 Contract research organization

PPD



14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div>Surveillance information entry times</div> <div>Items for surveillance</div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		← <input type="radio"/> →					<input type="radio"/>
	Use of concomitant drugs		← <input type="radio"/> →					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		← <input type="radio"/> <small>Note 5)</small> →					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		← <input type="radio"/> →					<input type="radio"/>
	Adverse events		← <input type="radio"/> →					<input type="radio"/>

○ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, or at treatment discontinuation).

Note 5) Within 1 month before the start of treatment to the end of the surveillance.

Drug Use Surveillance Protocol
Drug Use Surveillance for Takecab Tablets
Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 4
Preparation date	August 5, 2016

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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI [REDACTED]). Prior to starting this surveillance, an officer of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda officer) will provide the

surveillance investigator with an explanation about the objective and contents of this surveillance, CCI operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “CCI Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on CCI will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreements with the study site, the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into CCI and will provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator or a person designated by the surveillance investigator* will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator or a person designated by the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, the surveillance investigator or a person designated by the surveillance investigator will enter the observation results into CCI and the surveillance investigator will provide an electronic signature.

*The person designated by the surveillance investigator will be a person belonging to the medical institution [including those who have contract agreements with a medical institution such as a contract research organization (CRO)]. The physicians who are the surveillance directors (one will be appointed for each study site or its department at the time of conclusion of contract agreements) will prepare records of the designees and designation dates and (whatever the form is) provide a signature or a signature and a seal, and submit the records to a Takeda officer before the person designated by the surveillance investigator enters data into

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda officer. Upon request from a Takeda officer, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: March 2016 to April 30, 2018

Accrual period: March 2016 to February 28, 2018^{Note)}

^{Note)} Even for the patients with Takecab Tablets prescribed by February 28, 2018, patient enrollment (data entry in CCI) will not be accepted on and after March 1, 2018.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before February 28, 2018, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before February 28, 2018 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator or a person designated by the surveillance investigator will enter information on the items shown below into CCI. The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses

(excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

*1: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

*2: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

*3: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*1})

*1: Mild: Occasionally or slightly symptomatic.

Moderate: Considerably symptomatic.

Severe: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance*².

*²: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets*¹ to the end of the surveillance*²

*¹: Within 1 month before the start of treatment.

*²: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda officer. Upon request by the Takeda officer, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Unwanted symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company
- Unwanted symptoms that have developed in persons using the drug and have become known by a lawsuit or any other legal act

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”

1. Results in death (death)
2. Life-threatening (possible death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disorders)
5. Causes congenital anomalies
6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section

Takeda Medically Significant AE List

- | | |
|---|--|
| • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) | • Anaphylactic shock |
| • Torsades de pointes/ventricular fibrillation/ventricular tachycardia | • Acute renal failure |
| • Malignant hypertension | • Pulmonary hypertension |
| • Convulsive seizures (including convulsions and epilepsy) | • Pulmonary fibrosis (including interstitial pneumonia) |
| • Agranulocytosis | • Neuroleptic malignant syndrome/malignant hyperpyrexia |
| • Aplastic anemia | • Spontaneous abortions/stillbirths and fetal deaths |
| • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) | • Confirmed or suspected transmission of drug-mediated infection |
| • Acute hepatic failure | • Endotoxin shock or, suspected |
| • Hepatic necrosis | |

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance* will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance* will be tabulated by target disease.

*The time point will be Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, and, if treatment with Takecab Tablets is discontinued before these times, at the time of treatment discontinuation.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited
PPD

13.0 Contract research organization

PPD

14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div>Surveillance information entry times</div> <div>Items for surveillance</div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		◀────────○────────▶					<input type="radio"/>
	Use of concomitant drugs		◀────────○────────▶					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		◀────────○ <small>Note 5)</small> ────────▶					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		◀────────○────────▶					<input type="radio"/>
	Adverse events		◀────────○────────▶					<input type="radio"/>

○ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer, or at treatment discontinuation).

Note 5) Within 1 month before the start of treatment to the end of the surveillance.

Drug Use Surveillance Protocol

Drug Use Surveillance for Takecab Tablets

Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 3
Preparation date	January 7, 2016

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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI). Prior to starting this surveillance, an officer of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda officer) will provide the

surveillance investigator with an explanation about the objective and contents of this surveillance, CCI operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “CCI Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on CCI will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreements with the study site, the surveillance investigator or a person designated by the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into CCI and the surveillance investigator will provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator or a person designated by the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator or a person designated by the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and the surveillance investigator will provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, the surveillance investigator or a person designated by the surveillance investigator will enter the observation results into CCI and the surveillance investigator will provide an electronic signature.

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda officer. Upon request from a Takeda officer, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: March 2016 to April 30, 2018

Accrual period: March 2016 to February 28, 2018^{Note)}

Note) Even for the patients with Takecab Tablets prescribed by February 28, 2018, patient enrollment (data entry in CCI) will not be accepted on and after March 1, 2018.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before February 28, 2018, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before February 28, 2018 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator or a person designated by the surveillance investigator will enter information on the items shown below into CCI. The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses (excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose

of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

*1: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

*2: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

*3: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*})

*Mild: Occasionally or slightly symptomatic.

Moderate: Considerably symptomatic.

Severe: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance*.

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets*¹ to the end of the surveillance*²

*1: Within 1 month before the start of treatment.

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda officer. Upon request by the Takeda officer, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Unwanted symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company
- Unwanted symptoms that have developed in persons using the drug and have become known by a lawsuit or any other legal act

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”	
<ol style="list-style-type: none"> 1. Results in death (death) 2. Life-threatening (possible death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disorders) 5. Causes congenital anomalies 6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section 	
<u>Takeda Medically Significant AE List</u>	
<ul style="list-style-type: none"> • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) • Torsades de pointes/ventricular fibrillation/ventricular tachycardia • Malignant hypertension • Convulsive seizures (including convulsions and epilepsy) • Agranulocytosis • Aplastic anemia • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) • Acute hepatic failure • Hepatic necrosis 	<ul style="list-style-type: none"> • Anaphylactic shock • Acute renal failure • Pulmonary hypertension • Pulmonary fibrosis (including interstitial pneumonia) • Neuroleptic malignant syndrome/malignant hyperpyrexia • Spontaneous abortions/stillbirths and fetal deaths • Confirmed or suspected transmission of drug-mediated infection • Endotoxin shock or, suspected

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance will be tabulated by target disease.

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance will be tabulated by target disease.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited

PPD

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13.0 Contract research organization

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14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div> <div>Surveillance information entry times</div> <div>Items for surveillance</div> </div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		← <input type="radio"/> →					<input type="radio"/>
	Use of concomitant drugs		← <input type="radio"/> →					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		← <input type="radio"/> <small>Note 5)</small> →					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		← <input type="radio"/> →					<input type="radio"/>
	Adverse events		← <input type="radio"/> →					<input type="radio"/>

☐ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer) or treatment discontinuation.

Note 5) Within 1 month before the start of treatment to the end of the surveillance.

Drug Use Surveillance Protocol

Drug Use Surveillance for Takecab Tablets

Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 2
Preparation date	June 22, 2015

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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI [REDACTED]). Prior to starting this surveillance, an officer of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda officer) will provide the

surveillance investigator with an explanation about the objective and contents of this surveillance, CCI operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “CCI Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on CCI will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreements with the study site, the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into CCI and provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator will enter patient characteristics information, treatment information, and other information into CCI and provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, enter the observation results into CCI and provide an electronic signature.

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda officer. Upon request from a Takeda officer, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: March 2016 to April 30, 2018

Accrual period: March 2016 to February 28, 2018^{Note)}

^{Note)} Even for the patients with Takecab Tablets prescribed by February 28, 2018, patient enrollment (data entry in CCI will not be accepted on and after March 1, 2018.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before February 28, 2018, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before February 28, 2018 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator will enter information on the items shown below into CCI.

The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses (excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

^{*1}: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

^{*2}: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

^{*3}: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*})

^{*Mild}: Occasionally or slightly symptomatic.

^{Moderate}: Considerably symptomatic.

^{Severe}: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance^{*}.

^{*}The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets^{*1} to the end of

the surveillance*²

*1: Within 1 month before the start of treatment.

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda officer. Upon request by the Takeda officer, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events, whereas foreseeable exacerbations of the target disease will not be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for

duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Unwanted symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company
- Unwanted symptoms that have developed in persons using the drug and have become known by a lawsuit or any other legal act

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”

1. Results in death (death)
2. Life-threatening (possible death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disorders)
5. Causes congenital anomalies
6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section

Takeda Medically Significant AE List

- | | |
|---|--|
| • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) | • Anaphylactic shock |
| • Torsades de pointes/ventricular fibrillation/ventricular tachycardia | • Acute renal failure |
| • Malignant hypertension | • Pulmonary hypertension |
| • Convulsive seizures (including convulsions and epilepsy) | • Pulmonary fibrosis (including interstitial pneumonia) |
| • Agranulocytosis | • Neuroleptic malignant syndrome/malignant hyperpyrexia |
| • Aplastic anemia | • Spontaneous abortions/stillbirths and fetal deaths |
| • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) | • Confirmed or suspected transmission of drug-mediated infection |
| • Acute hepatic failure | • Endotoxin shock or, suspected |
| • Hepatic necrosis | |

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance will be tabulated by target disease.

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance will be tabulated by target disease.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited

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13.0 Contract research organization

PPD

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14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div>Surveillance information entry times</div> <div>Items for surveillance</div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		<div>← ○ →</div>					<input type="radio"/>
	Use of concomitant drugs		<div>← ○ →</div>					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		<div>← ○ <small>Note 5)</small> →</div>					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		<div>← ○ →</div>					<input type="radio"/>
	Adverse events		<div>← ○ →</div>					<input type="radio"/>

○ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer) or treatment discontinuation.

Note 5) Within 1 month before the start of treatment to the end of the surveillance.

Drug Use Surveillance Protocol
Drug Use Surveillance for Takecab Tablets
Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis

Sponsor	Takeda Pharmaceutical Company Limited
Protocol No.	Vonoprazan-5001
Version No.	Version 1
Preparation date	December 26, 2014

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1.0 Background

The safety of Takecab Tablets 20 mg in the treatment of gastric ulcer, duodenal ulcer, and reflux esophagitis has been assessed in Japanese clinical studies in 244, 183, and 988 patients, respectively, showing no remarkable problems. In postmarketing routine practices, however, unlike in the clinical studies, the drug may be used in patients with various complications and patients receiving multiple concomitant drugs, which means that the possibility of onset of unexpected adverse drug reactions cannot be ruled out based on the results of the clinical studies. Hence, we planned a drug use surveillance (hereinafter referred to as this surveillance) study to assess the safety and efficacy of Takecab Tablets in the three acid-related diseases gastric ulcer, duodenal ulcer, and reflux esophagitis in actual routine practices.

This surveillance will be conducted in compliance with the MHLW Ministerial Ordinance on GPSP and other related regulatory requirements.

2.0 Objective

To assess the safety and efficacy of Takecab Tablets in patients with gastric ulcer, duodenal ulcer, and reflux esophagitis in actual use settings and routine practices.

3.0 Planned sample size and justification

3.1 Planned sample size

3,000 Patients

The sample size will not be less than 500 patients for each of gastric ulcer and duodenal ulcer, and will not be less than 1,000 patients for reflux esophagitis.

3.2 Justification

Gastric ulcer, duodenal ulcer, and reflux esophagitis all share the same pathologic feature that gastrointestinal mucosal injury is caused by gastric acid. Duration of treatment in Japanese clinical studies of Takecab Tablets in various patient populations with each disease was roughly the same for gastric ulcer and reflux esophagitis (up to 8 weeks) and duodenal ulcer (up to 6 weeks), and incidences and severity of adverse drug reactions and safety profiles for adverse drug reactions with high incidences were similar.

Based on the above facts, a drug use-results surveillance study will be conducted with a planned sample size of 3,000 patients with the three acid-related diseases of gastric ulcer, duodenal ulcer, and reflux esophagitis. With regard to the minimum sample size allowing the safety of Takecab Tablets to be assessed in patients with each disease, we have decided to enroll at least 500 patients with gastric ulcer and duodenal ulcer. Since the number of patients with reflux esophagitis has been increasing rapidly year by year in Japan, and the disease is considered to affect the largest number of patients for whom Takecab Tablets is indicated, we have decided to enroll at least 1,000 patients with reflux esophagitis. Hence, incidences and severity of adverse drug reactions and differences in major adverse drug reactions in actual use settings and routine practices seem to be assessable by disease (the sample size was not statistically calculated).

4.0 Subject patients

Patients with gastric ulcer, duodenal ulcer, and reflux esophagitis will be enrolled. However, the subjects should not meet any of the exclusion criteria shown below. Refer to the Precautions in the package insert.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the subjects of this surveillance.

- 1) Patients with a past medical history of hypersensitivity to any of the ingredients of Takecab Tablets
- 2) Patients on treatment with atazanavir sulfate or rilpivirine hydrochloride
- 3) When the target disease for Takecab Tablets is gastric ulcer or duodenal ulcer, patients whose endoscopic stage classification by Sakita and Miwa at the start of treatment with Takecab Tablets is the scarring stage (S1, S2)
- 4) When the target disease for Takecab Tablets is reflux esophagitis, patients whose rating by the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara) at the start of treatment with Takecab Tablets is Grade N or Grade M

5.0 Dosage and administration

The usual adult dosage is 20 mg of vonoprazan administered orally once daily. Usually, the duration of treatment should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer. For reflux esophagitis, the duration of treatment should usually be up to 4 weeks; if the effect is insufficient, however, the drug can be administered for up to 8 weeks. Refer to the Precautions in the package insert.

6.0 Planned number of medical institutions by department

Gastroenterology and other departments: About 500 medical institutions

7.0 Methods

7.1 Duration of observation

Duration of observation will be 8 weeks for gastric ulcer and reflux esophagitis and 6 weeks for duodenal ulcer.

However, if treatment with Takecab Tablets is completed with the goal of treatment attained, or treatment with Takecab Tablets is discontinued for any reason, the surveillance will be ended at that time.

7.2 Requests to, and agreements with, study sites

Requests to, and agreements with, study sites will be made using a web-based electronic data collection system (CCI). Prior to starting this surveillance, a medical representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda MR) will provide

the surveillance investigator with an explanation about the objective and contents of this surveillance, [CCI] operating procedures, electronic signature, user ID, and handling of passwords using the documents “Request for Your Cooperation in Drug Use-Results Surveillance,” “Implementation Guideline,” “Input Screen Image,” and “[CCI] Operating Manual (Abridged Edition)” and conclude written agreements with the study site to ask it to conduct the surveillance within the specified surveillance period.

7.3 Patient registration

“Central registration” based on [CCI] will be used. For the patients with Takecab Tablets prescribed on or after the starting day of the period of agreement with the study site, the surveillance investigator will enter patient enrollment information (refer to Section 9.1) into [CCI] and provide an electronic signature not later than 14 days after the day of prescribing Takecab Tablets (the prescribing day is defined as “Day 0” and the day after the prescribing day as “Day 1”).

7.4 Data entry in the surveillance form (electronic) and electronic signature

For all the patients enrolled, the surveillance investigator will enter patient characteristics information, treatment information, and other information into [CCI] and provide an electronic signature generally within 1 month after the end of the observation period for each patient. If Takecab Tablets are not confirmed to have actually been taken, this fact will be entered (no other items need to be entered).

For the patients who have discontinued Takecab Tablets for any reason during the observation period, the surveillance investigator will enter patient characteristics information, treatment information, and other information into [CCI] and provide an electronic signature generally within 1 month after completion of the observations required. For the patients who have discontinued Takecab Tablets because of development of any adverse event, however, the surveillance investigator will continue observations until the adverse event resolves or remits whenever possible after treatment discontinuation, enter the observation results into [CCI] and provide an electronic signature.

7.5 Measures to be taken in case of serious adverse events

If any serious adverse event develops during the observation period, the surveillance investigator will immediately notify this fact to a Takeda MR. Upon request from a Takeda MR, the surveillance investigator will separately provide detailed information.

8.0 Scheduled period

Surveillance period: September 2015 to October 31, 2017

Accrual period: September 2015 to August 31, 2017^{Note)}

^{Note)} Even for the patients with Takecab Tablets prescribed by August 31, 2017, patient enrollment (data entry in [CCI]) will not be accepted on and after September 1, 2017.

If the number of enrolled patients reaches the planned sample size for this surveillance as a whole before August 31, 2017, registration will be terminated before the end of the patient accrual period. If the patient accrual period is shortened, the overall surveillance period will be changed in proportion to the shortage.

In addition, enrollment may be subject to limitations for each target disease before August 31, 2017 in view of the enrollment status for each target disease.

9.0 Items for surveillance

The surveillance investigator will enter information on the items shown below into CCI.
The schedule for this surveillance is shown in the Appendix.

9.1 Patient enrollment

1) Items for surveillance

Date of prescribing Takecab Tablets, patient ID No., initialized patient name, sex, date of birth, target disease for Takecab Tablets, exclusion criteria ratings

2) Surveillance times

At the time of patient enrollment

9.2 Patient demographic information

1) Items for surveillance

Date of diagnosing the target disease, Inpatient/outpatient classification (from the start of treatment with Takecab Tablets), predisposition to hypersensitivity (presence/absence and details), complications (presence/absence and details), past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis (presence/absence and details), height, body weight, presence/absence of *Helicobacter pylori* infection (from the start of treatment with Takecab Tablets), presence/absence of esophageal hiatal hernia, smoking history, drinking history, treatments prior to the start of Takecab Tablets [presence/absence, names of drugs, doses (excluding H2 blockers), and duration of treatment]

2) Surveillance times

At the start of treatment with Takecab Tablets

9.3 Treatment information

1) Items for surveillance

Use of Takecab Tablets (daily dose, duration of treatment, and reason for treatment discontinuation), use of concomitant drugs (presence/absence, names of drugs, and purpose of administration)

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4 Items for examination and observation

9.4.1 Endoscopy

1) Items for examination

Endoscopy (check date and findings^{*1})

^{*1}: Gastric ulcer and duodenal ulcer will be assessed using the endoscopic stage classification by Sakita and Miwa, and reflux esophagitis will be assessed using the classification of mucosal injuries according to the Los Angeles Classification of Gastroesophageal Reflux Disease (modified by Hoshihara).

2) Surveillance times

Examination time points at the start of treatment with Takecab Tablets^{*2} and the end of the surveillance^{*3}

^{*2}: The time point will be essentially between 7 days before the start of treatment and the day of the start of treatment.

^{*3}: The time point will be essentially until 14 days after Week 8 for gastric ulcer and reflux esophagitis and after Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the time point will be essentially until 14 days after treatment discontinuation.

9.4.2 Subjective symptoms (heartburns, acid reflux, postprandial heavy stomach feeling, early satiety, epigastralgia, epigastric burning, sensation of abdominal distention, nausea/vomiting, burping, anorexia)

1) Items for observation

Subjective symptoms (presence/absence and severity^{*})

^{*Mild}: Occasionally or slightly symptomatic.

^{Moderate}: Considerably symptomatic.

^{Severe}: Unendurably symptomatic.

2) Surveillance times

Interview time points at the start of treatment with Takecab Tablets, at Week 2, at Week 4, and at the end of the surveillance^{*}.

^{*}The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.3 Liver function test

1) Parameters

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

2) Surveillance times

Examination time points from the start of treatment with Takecab Tablets^{*1} to the end of

the surveillance*²

*1: Within 1 month before the start of treatment.

*2: The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.4.4 Other items for observation

1) Items for observation

Presence/absence of pregnancy during the observation period (for women only)

If the subject is found to be pregnant during the observation period, this fact should immediately be notified to a Takeda MR. Upon request by the Takeda MR, the surveillance investigator will provide detailed information (including information up to delivery, including details of premature birth and other outcomes) separately using a pregnant-woman sheet.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

9.5 Adverse events

1) Items for surveillance

Presence/absence of adverse events (see Table 1), names of adverse events, onset days, seriousness and rationale for the seriousness rating (see Table 2), cause of discontinuation of Takecab Tablets, outcome determination day, outcome, causality with Takecab Tablets* (see Table 3).

If the outcome is “unresolved” or “unknown” and if the causality is indeterminable, a follow-up surveillance will be performed whenever possible.

In the event of manifested hepatic dysfunction or gastrointestinal infections with *Clostridium difficile*, detailed information (clinical courses, results of tests performed for diagnostic purposes, etc.) will be collected as much as possible.

*If the rating of causality with Takecab Tablets is “unrelated”, information on the justification for the rating will be collected. If the rating is “indeterminable”, the reason will be recorded.

Note) Matters to be taken into account with regard to adverse events

Abnormal exacerbations of the target disease, including those exceeding the foreseeable spontaneous course of the condition, will be handled as adverse events, whereas foreseeable exacerbations of the target disease will not be handled as adverse events.

2) Surveillance times

From the start of treatment with Takecab Tablets to the end of the surveillance*

*The end of the surveillance will be at Week 8 for gastric ulcer and reflux esophagitis and Week 6 for

duodenal ulcer. If Takecab Tablets are discontinued before these times, the end of the surveillance will be at the time of treatment discontinuation.

Table 1 Definition of an adverse event

An adverse event (AE) refers to any unwanted medical event appearing in a patient receiving a drug. An AE does not always represent an event for which causality with administration of the drug is evident.

Hence, an adverse event refers to any unwanted or unintended sign (including abnormal laboratory values), symptom, or disease that has occurred in a subject receiving the test drug, irrespective of the presence/absence of causality with the drug.

The following cases will also be handled as adverse events:

- Symptoms etc. that have developed in infants breastfed by mothers on treatment with the drug
- Symptoms etc. that have developed in children receiving the drug
- Symptoms etc. that have developed with occupational exposure to the drug
- Symptoms etc. that have developed with administration of a false drug imitating an ethical drug marketed by our company

Table 2 Seriousness rating criteria

If any of the following criteria applies, the event will be rated as “serious.”

1. Results in death (death)
2. Life-threatening (possible death)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospital admission or prolonged hospitalization)
4. Results in persistent or significant disability/incapacity (disorders)
5. Causes congenital anomalies
6. Medically important states secondary to Items 1 to 5 AEs included in the “Takeda Medically Significant AE List” will be included in this section

Takeda Medically Significant AE List

- | | |
|---|--|
| • Acute respiratory insufficiency/acute respiratory distress syndrome (ARDS) | • Anaphylactic shock |
| • Torsades de pointes/ventricular fibrillation/ventricular tachycardia | • Acute renal failure |
| • Malignant hypertension | • Pulmonary hypertension |
| • Convulsive seizures (including convulsions and epilepsy) | • Pulmonary fibrosis (including interstitial pneumonia) |
| • Agranulocytosis | • Neuroleptic malignant syndrome/malignant hyperpyrexia |
| • Aplastic anemia | • Spontaneous abortions/stillbirths and fetal deaths |
| • Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome) | • Confirmed or suspected transmission of drug-mediated infection |
| • Acute hepatic failure | • Endotoxin shock or, suspected |
| • Hepatic necrosis | |

Table 3 Acceptance criteria for causality between adverse events and Takecab Tablets

Rating	Acceptance criteria
Related	A temporal correlation (including post-discontinuation courses) is found. Alternatively, although other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures, may also be involved, the event is attributable to the study drug.
Unrelated	No temporal correlation with the drug is found. Alternatively, the event is reasonably attributable to other factors, such as primary disease, complications, concomitant drugs, and concomitant procedures.
Indeterminable	Information essential for assessments, such as temporal correlations (including post-discontinuation courses), primary disease, complications, concomitant drugs, and concomitant procedures, are lacking.

10.0 Analysis items and methods

10.1 Items concerning study population composition

Number of patients enrolled, number of patients from whom the surveillance form (electronic) has been collected, numbers of patients included in the safety and efficacy analysis sets, number of patients excluded from analysis and reasons for removal, and other items will be tabulated.

10.2 Patient demographics

Data on patient demographics, including sex, age, predisposition to hypersensitivity, and complications, will be tabulated.

10.3 Treatment details

Data on the use of Takecab Tablets and the use of concomitant drugs will be tabulated.

10.4 Matters concerning the safety

Data for the safety analysis set will be tabulated as follows: AEs will be reworded using the MedDRA/J and summarized with Preferred Term (PT) and System Organ Class (SOC).

10.4.1 Factors of onset of adverse events

With regard to the adverse events occurring during the observation period, frequency data will be tabulated by type, onset time, seriousness, causality with Takecab Tablets, and other aspects.

10.4.2 Factors that may affect the safety

With regard to the adverse drug reactions occurring during the observation period, frequency data will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets and use of concomitant drugs).

10.5 Matters concerning the safety

Data for the efficacy analysis set will be tabulated as follows:

10.5.1 Endoscopic cure rate

Data on endoscopic cure rates in patients with endoscopic findings available at the start of treatment with Takecab Tablets and the end of the surveillance will be tabulated by target disease.

10.5.2 Subjective symptom amelioration rate

Data on subjective symptom amelioration rates in patients with severity findings available from the start of treatment with Takecab Tablets to the end of the surveillance will be tabulated by target disease.

10.5.3 Factors that may affect the efficacy

Data on endoscopic cure rates and subjective symptom amelioration rates will be tabulated by target disease, patient demographic factors (sex, age, presence/absence of complicating renal dysfunction, presence/absence of complicating hepatic dysfunction, etc.), and treatment (use of Takecab Tablets, use of concomitant drugs).

11.0 Surveillance information registry

Takeda Pharmaceutical Company Limited will register information on this surveillance study prior to its start date with an open-access website.

- Japan Pharmaceutical Information Center Clinical Trials Information
- US National Institutes of Health (NIH) Clinical Study Registration System: [ClinicalTrials.gov](https://clinicaltrials.gov)

12.0 Organizational structure

12.1 Manager

Takeda Pharmaceutical Company Limited

PPD



13.0 Contract research organization

PPD



14.0 Other requirements

14.1 Protocol revisions

Study progression, onset of adverse drug reactions and serious adverse drug reactions that are unexpected from the Precautions, presence/absence of increased incidences of particular adverse drug reactions, validity of survey items, etc. will be monitored during the survey period and, if necessary, this protocol will be reconsidered and revised. If partial changes in the dosage

and administration or indications are approved during the surveillance period, the necessity for revising this protocol will be determined as required, and the protocol will be revised if necessary.

14.2 Measures to be taken in the event of problematic or doubtful issues

If any problematic finding is found regarding safety and efficacy, the data will be checked extensively, and appropriate countermeasures will be considered.

Appendix: Schedule of observations

<div>Surveillance information entry times</div> <div>Items for surveillance</div>		Duration of observation						
		At the time of patient enrollment	At the start of treatment with Takecab Tablets	Week 2	Week 4	Week 6 <small>Note 1)</small>	Week 8 <small>Note 2)</small>	At the time of treatment discontinuation
Patient enrollment	Date of prescribing Takecab Tablets	<input type="radio"/>						
	Patient ID No.	<input type="radio"/>						
	Initialized name of patient	<input type="radio"/>						
	Sex	<input type="radio"/>						
	Date of birth	<input type="radio"/>						
	Target disease for Takecab Tablets	<input type="radio"/>						
	Exclusion criteria rating	<input type="radio"/>						
Patient demographic information	Date of diagnosing the target disease		<input type="radio"/>					
	Inpatient/outpatient classification		<input type="radio"/>					
	Hypersensitivity predisposition		<input type="radio"/>					
	Complications		<input type="radio"/>					
	Past medical history of gastric ulcer/duodenal ulcer/reflux esophagitis		<input type="radio"/>					
	Height, weight		<input type="radio"/>					
	Presence/absence of <i>Helicobacter pylori</i> infection		<input type="radio"/>					
	Presence/absence of esophageal hiatal hernia		<input type="radio"/>					
	Smoking history		<input type="radio"/>					
	Drinking history		<input type="radio"/>					
	Treatment prior to starting Takecab Tablets		<input type="radio"/>					
Treatment information	Use of Takecab Tablets		◀────────○────────▶					<input type="radio"/>
	Use of concomitant drugs		◀────────○────────▶					<input type="radio"/>
Items for examination and observation	Endoscopy		<input type="radio"/> <small>Note 3)</small>			<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>	<input type="radio"/> <small>Note 4)</small>
	Severity of subjective symptoms		<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Liver function test		◀────────○ <small>Note 5)</small> ────────▶					<input type="radio"/>
	Presence/absence of pregnancy (for women only)		◀────────○────────▶					<input type="radio"/>
	Adverse events		◀────────○────────▶					<input type="radio"/>

○ : Performed.

◄ ○ ► : Performed throughout the surveillance period.

Note 1) Gastric ulcer and reflux esophagitis are excluded.

Note 2) Duodenal ulcer is excluded.

Note 3) The time point will be essentially from 7 days before the start of treatment to the treatment start day.

Note 4) The time point will be essentially until 14 days after the end of the surveillance (Week 8 for gastric ulcer and reflux esophagitis and Week 6 for duodenal ulcer) or treatment discontinuation.

Note 5) Within 1 month before the start of treatment to the end of the surveillance.