Title: Drug use surveillance of Takecab tablets "Supplement to Helicobacter pylori eradication"

NCT Number: NCT03219723

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

Protocol of drug use surveillance

Drug use surveillance of Takecab tablets

“Supplement to *Helicobacter pylori* eradication”

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vonoprazan-5002**
Version	**Version 5**
Date	**February 23, 2018**

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1.0 Background of conduct

In the domestic clinical studies of *Helicobacter Pylori* (*H. pylori*) eradication with Takecab Tablets in combination with antimicrobials, safety of triple therapy was evaluated: Takecab Tablets, amoxicillin and clarithromycin (first-line eradication) in 329 patients, and Takecab Tablets, amoxicillin and metronidazole (second-line eradication) in 50 patients, and the results showed no specific issue.

The safety profile of the first-line eradication could be expected in view of the results of Takecab Tablets clinical studies in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis) and information provided in the package inserts of antimicrobials. Most of the adverse reactions (ADRs) developed during the second-line eradication were also observed in the first-line eradication, and there was no substantial difference between them. Accordingly, the safety profile of the use of Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.

The Drug use surveillance of Takecab Tablets (this survey) for the supplement to *H. pylori* eradication in first-line and second-line eradication in the routine clinical setting is planned to confirm validity of this estimation (whether there is a new safety concern or not).

This survey is conducted in compliance with relevant regulatory requirements such as GPSP ministerial ordinance.

2.0 Objectives

The objective of this survey is to evaluate the safety and efficacy of first-line and second-line eradication including Takecab Tablets (triple therapy) in the routine clinical setting.

3.0 Planned sample size and its rationale

3.1 Sample size

500 patients

3.2 Rationale

The safety profile of *H. pylori* eradication with a proton pump inhibitor (lansoprazole) in combination with antimicrobials (amoxicillin and clarithromycin) observed in the domestic clinical studies and the drug use surveillance could be expected from the results of the domestic clinical studies and the drug use surveillance of lansoprazole in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis), and from the information provided in the package inserts of antimicrobials.

The safety profile of the first-line eradication observed in the clinical studies for *H. pylori* eradication with Takecab Tablets in combination with antimicrobials could be expected from

the results of the clinical studies of Takecab Tablets in patients with acid-related diseases and information provided in the package inserts of antimicrobials.
Based on the above, the safety profile of the first-line eradication with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.
In addition, it has been confirmed that ADRs of *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and metronidazole) in the specific drug use surveillance of proton pump inhibitors (lansoprazole, omeprazole and rabeprazole) were mostly similar to the ADRs reported in *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and clarithromycin). Most of the ADRs developed during the second-line *H. pylori* eradication in the clinical study of Takecab Tablets in combination with antimicrobials were also observed in the first-line eradication. Therefore, it is estimated that ADRs developed in association with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication are not substantially different between first-line eradication and second-line eradication. In view of the above, the drug use surveillance of Takecab Tablets for supplement of *H. pylori* eradication is to be conducted for both first-line and second-line eradication.
Accordingly, in this survey, data will be collected from 500 patients to whom Takecab Tablets is administered for supplement of *H. pylori* eradication, and will be compared with the safety information of Takecab Tablets collected in the drug use surveillance in patients with acid-related diseases (total 3,000 patients) and with information provided in the package inserts of antimicrobials, and it will be confirmed whether there is a new safety concern or not (please note that the sample size of 500 patients is not statistically calculated).
In this survey, patients excluded from the clinical studies such as with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis will be enrolled.

4.0 Study population

Patients with the diseases described below* will receive triple therapy for *H. pylori* eradication. However, patients should meet the inclusion criterion and should not meet the exclusion criterion described below. Refer to the Precautions section of the package insert.

* If a patient's first-line eradication is unsuccessful in this survey, the patient can be enrolled in the second-line eradication in this survey.

Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis

4.1 Inclusion criteria

Patients who meet either of the following criteria will be included in the survey:

[1] Patients receiving *H. pylori* eradication for the first time

[2] Patients for whom *H. pylori* eradication with Takecab Tablets or proton pump inhibitor + amoxicillin + clarithromycin was found unsuccessful and who are to receive eradication treatment with amoxicillin and metronidazole

4.2 Exclusion criteria

Patients who meet either of the following criteria will not be included in the survey. Refer to the Contraindications and Precautions section of the package insert of antimicrobials used in the triple therapy.

[1] Patients with previous history of hypersensitivity to ingredients in Takecab Tablets

[2] Patients receiving atazanavir sulfate or rilpivirine hydrochloride

5.0 Dosage and administration

The usual dose for adults is 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. These three drugs will be orally administered at the same time, twice daily for 7 days. The dose of clarithromycin can be increased as clinically warranted. However, the dosage of clarithromycin should not exceed 400 mg (potency)/dose twice daily.

If *H. pylori* eradication with a three-drug regimen comprising vonoprazan or proton pump inhibitor + amoxicillin hydrate + clarithromycin is unsuccessful, as an alternative treatment, the following three drugs will be orally administered to adults at the same time, twice daily for 7 days: vonoprazan at a dose of 20 mg, amoxicillin hydrate at a dose of 750 mg (potency), and metronidazole at a dose of 250 mg. Refer to the Precautions section of the package insert of antimicrobials used in triple therapy.

6.0 Number of medical institutions by departments where the survey is planned

Internal medicine department (such as gastrointestinal medicine department)	Approximately 150 medical institutions
Hematology department	Approximately 10 medical institutions

7.0 Method

7.1 Observational period

Triple therapy period (7 days) and the period from the completion of the triple therapy to the determination of *H. pylori* eradication

Time frame of the *H. pylori* determination is approximately from 4 weeks* to 2 months after the triple therapy.

* According to the "Guidelines for diagnosis and treatment of *H. pylori* infection" of the Japanese Society for *Helicobacter* Research, determination of *H. pylori* eradication should be conducted after 4 weeks

from discontinuation of eradication therapy.

7.2 Request to and contract with the medical institutions

Request to and contract with the medical institutions will be conducted using web-based electronic data collection system (CCI). The Medical Representative of PPD will explain objectives and details of this survey, procedure, electronic signature, and handling of user ID and password of CCI to the surveillance investigator based on “Implementation guidance”, “Data entry screens of CCI ” and “CCI operational manual” when this survey is requested. Thereafter, written contract is made with the medical institution and conduct of the survey will be requested within the prespecified duration of the survey.

7.3 Method of patient enrollment

Patients will be enrolled with “central enrollment method” using CCI . The surveillance investigator will enter the information required for patient enrollment (see Section 9.1) and will provide his/her electronic signature in CCI concerning patients to whom drugs of triple therapy (three drugs including Takecab Tablets) are prescribed within 5 days after prescription day of the three drugs including Takecab Tablets (the prescription day is defined as “Day 0”, and the day after prescription as “Day 1”) after term of contract with the medical institution is started.

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

The surveillance investigator will enter the information of patient demographics and treatment and will provide electronic signature in CCI for all patients enrolled in this survey by one month after completion of the observational period of each patient. If receipt of Takecab Tablets was not confirmed, it will be entered so in CCI (it is not required to enter other data).

For the patients who discontinued triple therapy including Takecab Tablets for any reason during the observational period, the surveillance investigator will enter the information of patient demographics and treatment and will provide his/her electronic signature in CCI by one month after completion of required observation. However, for patients who discontinued triple therapy including Takecab Tablets due to development of an AE, observation will be continued as much as possible until resolve or resolving from the AE even after the treatment is discontinued, and the observation results will be entered in CCI with his/her electronic signature.

7.5 Actions to take at the time of development of a serious adverse event

The surveillance investigator will immediately communicate PPD on development of a serious adverse event during the observational period. In addition, the surveillance investigator will provide detailed information separately if requested by PPD

8.0 Scheduled period of the survey

Duration of the survey: September 2015 to April 30, 2017

Patient enrollment period: September 2015 to February 28, 2017 Note)

Note) Patients will not be enrolled in this survey (or entered in CCI) on or after March 1, 2017 even if Takecab Tablets is prescribed on or before February 28, 2017.
If enrollment of the planned number of patients of this survey is completed prior to February 28, 2017, the patient enrollment will be discontinued prior to the end of the patient enrollment period. When the patient enrollment period is shortened, the duration of the survey is to be changed according to the shortened period.

9.0 Data to be collected

The surveillance investigator will enter the information of the following items in CCI . The schedule of this survey is presented in the Appendix.

9.1 Patient enrollment

1) Data to be collected

Prescription date of the three drugs including Takecab Tablets used in the triple therapy; patient identification number; patient initials; sex; date of birth; target disease of *H. pylori* eradication; assessment of inclusion and exclusion criteria

2) Data collection period

At the time of patient enrollment

9.2 Patient demographic information

1) Data to be collected

Inpatient/outpatient classification (at the time when triple therapy is started); predisposition of hypersensitivity (presence/absence and details); complication (presence/absence and details); details of previous *H. pylori* eradication (in patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor with amoxicillin and clarithromycin); height; weight; smoking history; drinking history; diagnosis of *H. pylori* infection (time of diagnosis and testing method)

2) Data collection period

At the start of triple therapy

9.3 Information of treatment

1) Data to be collected

Treatment compliance to Takecab Tablets and antimicrobials used for triple therapy (name of drugs; daily dose; duration of triple therapy and reason for discontinuation of the triple therapy); treatment compliance to concomitant drugs (excluding antimicrobials used for the triple therapy) (presence/absence; drug name(s), and indication(s))

2) Data collection period

Duration from the start to the completion (or the discontinuation) of triple therapy

9.4 Test/examination items

9.4.1 Determination of *H. pylori* eradication

1) Test items

Conduct of tests (presence/absence; reason if test is not conducted; testing method; date and result of determination)

2) Testing period

At the time of determination of *H. pylori* eradication*

* Time frame of the *H. pylori* determination is approximately from 4 weeks to 2 months after the triple therapy.

9.4.2 Liver function test

1) Test items

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

2) Testing period

Duration from the start of triple therapy* to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

* Within 1 month before starting triple therapy

9.4.3 Other examination items

1) Examination items

Presence/absence of pregnancy during the observational period (only female patients)

If pregnancy is confirmed during the observational period, the information is immediately communicated to PPD. The surveillance investigator provides detailed information (including information until delivery, e.g., pregnancy outcome such as premature delivery, as much as possible) separately when PPD requests it.

2) Examination period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

9.5 Adverse event

1) Data to be collected

Presence/absence of adverse event (AE) (See Table 1); AE term; onset date; seriousness and reason for seriousness (See Table 2); cause of discontinuation of triple therapy; outcome date; outcome; causality* with triple therapy (See Table 3)

Follow-up survey will be conducted as much as possible when outcome is not resolved or unknown and causality is determined as unassessable.

Detailed information (e.g., clinical course and results of tests conducted for diagnosis) will be collected as much as possible when onset of hepatic function disorder or gastrointestinal infection of clostridium difficile is observed.

* Following information will be collected: rationale of assessment when causality is assessed as not related, and reason when causality is determined as unassessable.

Note) A point to consider concerning adverse events

Abnormal exacerbation of the target disease, i.e., exacerbation worse than the expected natural course of the disease, will be handled as an adverse event.

2) Data collection period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

Table 1 Definition of adverse event

Adverse event (AE) is any unfavorable medical occurrence in a patient administered a pharmaceutical product. It does not necessarily need to have a causal relationship with the pharmaceutical product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory values), symptom, or disease occurring at the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Following cases should also be handled as adverse events. • Symptoms developed in an infant breastfed by a mother receiving the pharmaceutical product • Unfavorable symptoms, etc. developed in a child after administration of the pharmaceutical product • Symptoms developed after occupational exposure to the pharmaceutical product • Symptoms developed due to the use of a counterfeit of a pharmaceutical product manufactured/marketed by Takeda Pharmaceutical Company Limited • Unfavorable symptoms developed in a user of the pharmaceutical product which information was obtained through litigation or other legal actions

Table 2 Seriousness assessment criteria

An event meeting any of the following criteria is assessed as "serious":

1. Fatal (death)
2. Life-threatening (life-threatening)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Congenital anomaly/birth defect (congenital anomaly)
6. Other medically important condition than 1-5. Events listed in "Takeda Medically Significant AE List" are included in this criterion.

Takeda Medically Significant AE List

- Acute respiratory failure/Acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes/Ventricular fibrillation/Ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Neuroleptic malignant syndrome/hyperthermia malignant
- Aplastic anaemia
- Abortion spontaneous/stillbirth and dead foetus
- Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Transmission or suspected transmission of infection via a medicinal product
- Hepatic necrosis
- Endotoxic shock or suspected endotoxic shock
- Acute hepatic failure

Table 3 Causality assessment criteria for adverse events and triple therapy

Assessment	Assessment criteria
Related	There is temporal relationship (including the clinical course after the discontinuation of the triple therapy). Or, while other factors such as underlying disease, complication, concomitant drug or concomitant procedure could be presumed, the AE is possibly related to triple therapy.
Not related	There is no temporal relationship with the triple therapy. Or, other factors such as underlying disease, complication, concomitant drug or concomitant procedure are quite considerable as the cause.
Unassessable	Information required for causality assessment, such as temporal relationship (including the clinical course after the discontinuation of the triple therapy), underlying disease, complication, concomitant drug, and concomitant procedure is insufficient.

10.0 Analysis items and method

10.1 Items related to patient disposition

Following data will be accumulated: number of patients enrolled; number of patients whose survey form (electronic) have been collected; number of patients in the safety analysis set and the efficacy analysis set; number of patients excluded from analysis and reasons for exclusion

10.2 Patient demographics

Patient demographic data including sex, age, hypersensitivity predisposition and complication will be accumulated.

10.3 Details of treatment

Treatment compliance to Takecab Tablets and antimicrobials used for the triple therapy and concomitant drugs (other than antimicrobials used for the triple therapy) will be accumulated.

10.4 Items related to safety

Following data will be accumulated for the safety analysis set. Adverse events are coded with MedDRA/J, and accumulated by Preferred Term (PT) and System Organ Class (SOC).
The patients enrolled to this survey in both first-line and second-line eradication cases will be accumulated separately.

10.4.1 Onset of adverse events

Frequencies of adverse events which developed during the observational period will be accumulated by type, onset period, seriousness, and causality with the triple therapy.

10.4.2 Factors which may affect safety

Frequencies of adverse reactions which developed during the observational period will be accumulated by subgroups of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; presence/absence of renal disorder complication; and presence/absence of liver disorder complication) and details of treatment (first-line and second-line eradication).

10.5 Items related to efficacy

Following data will be accumulated for the efficacy analysis set.

10.5.1 Eradication rate of *H. pylori*

In patients who have the result of determination of eradication, proportion of patients with *H. pylori* negative (eradication rate) will be accumulated by first-line and second-line eradication.

10.5.2 Factors which may affect efficacy

The eradication rates of *H. pylori* will be accumulated by subgroup of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; complication).

11.0 Registration of survey information

Takeda Pharmaceutical Company Limited will register information of this survey on the public websites before starting this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information

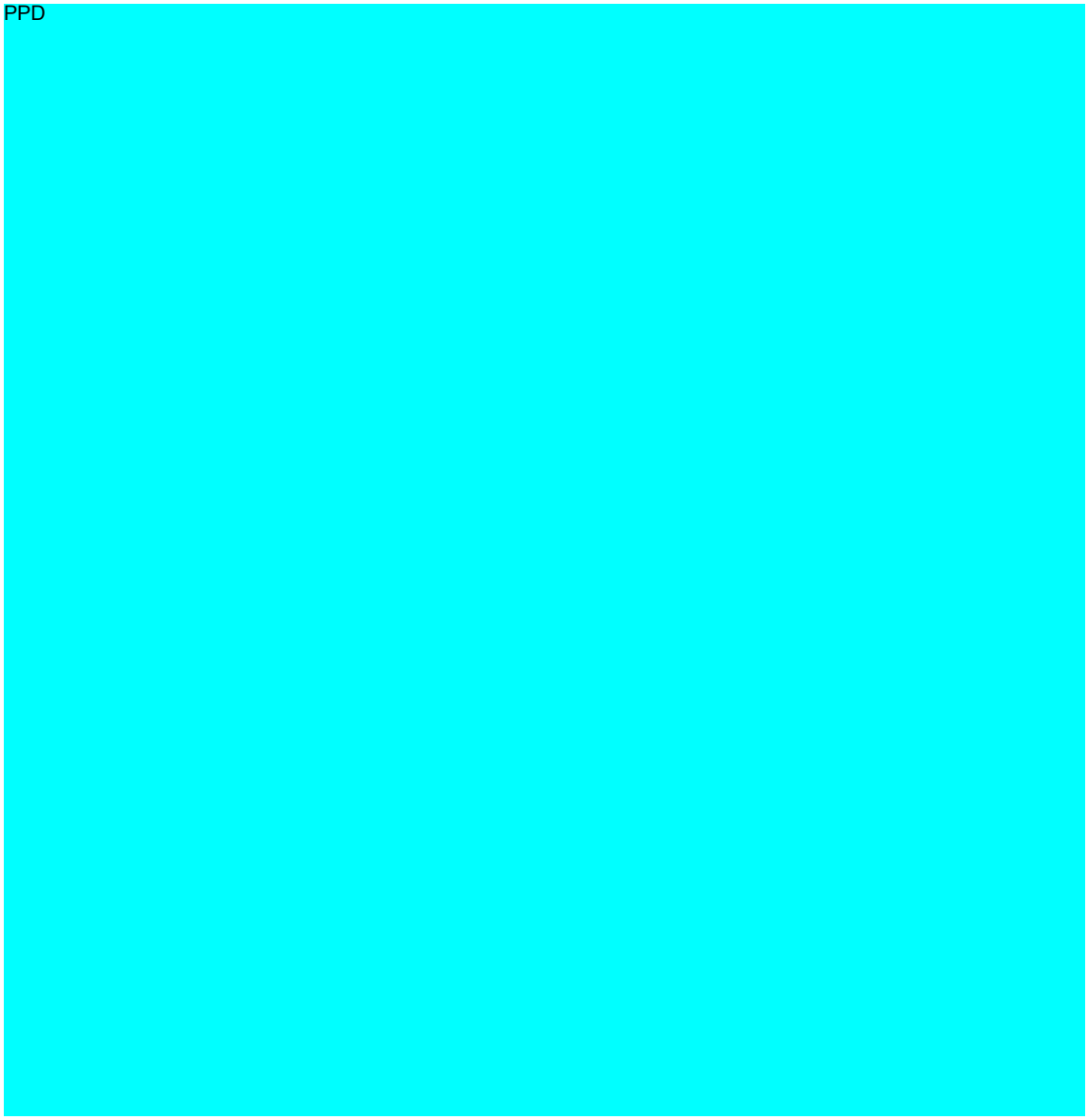
12.0 Organization of this survey

12.1 Manager

Takeda Pharmaceutical Company Limited

Post-marketing surveillance manager

13.0 Clinical research organizations



14.0 Other required items

14.1 Revision of the protocol

During the period of conducting this survey, following information will be captured: development of ADRs not expectable from Precautions for Use and onset of serious ADRs; whether there is increased frequency of specific ADRs or not; validity of the survey items. The protocol will be reviewed and revised if it is considered necessary. In addition, if a supplemental approval of a new dosage and administration or a new indication is granted during the period of conducting this survey, necessity of revision of the protocol will be examined if needed, and the protocol will be revised if needed.

14.2 Procedure when there is any issue or doubt

If there is any safety or efficacy issue, data will be closely examined, and action will be considered.

Appendix: Observation schedule

Data to be collected \ Period of survey/data entry		Observational period				
		At the time of patient enrollment	At the start of triple therapy	At the completion of triple therapy	At the time of determination of *H. pylori* eradication Note 1)	At the time of discontinuation of triple therapy
Patient enrollment	Prescription date of 3 drugs including Takecab Tablets in triple therapy	○				
	Patient identification number	○				
	Patient initials	○				
	Sex	○				
	Date of birth	○				
	Target disease of *H. pylori* eradication	○				
	Assessment of inclusion criteria	○				
	Assessment of exclusion criteria	○				
Patient demographic information	Inpatient/outpatient classification		○			
	Hypersensitivity predisposition		○			
	Complication		○			
	Previous *H. pylori* eradication Note 2)		○			
	Height, weight		○			
	Smoking history		○			
	Drinking history		○			
	Diagnosis of *H. pylori* infection		○			
Information of treatment	Treatment compliance to Takecab Tablets and antimicrobials		←○→			○
	Treatment compliance to concomitant drugs (excluding antimicrobials)		←○→			○
Test/ examination items	Determination of *H. pylori* eradication				○	
	Liver function test		←○Note 3)→			○
	Presence/absence of pregnancy (only female patients)		←○→			○
	Adverse event		←○→			○

○ : To be conducted

←○→ : To be conducted throughout the period

Note 1) Approximately from 4 weeks to 2 months after the triple therapy is completed

Note 2) In patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor in combination with amoxicillin and clarithromycin

Note 3) From within one month before the start of triple therapy to determination of *H. pylori* eradication

Protocol of drug use surveillance

Drug use surveillance of Takecab tablets

"Supplement to *Helicobacter pylori* eradication"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vonoprazan-5002**
Version	**Version 4**
Date	**June 2, 2017**

Table of contents

1.0 Background of conduct

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The Drug use surveillance of Takecab Tablets (this survey) for the supplement to *H. pylori* eradication in first-line and second-line eradication in the routine clinical setting is planned to confirm validity of this estimation (whether there is a new safety concern or not).

This survey is conducted in compliance with relevant regulatory requirements such as GPSP ministerial ordinance.

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* If a patient's first-line eradication is unsuccessful in this survey, the patient can be enrolled in the second-line eradication in this survey.

Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis

4.1 Inclusion criteria

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Internal medicine department (such as gastrointestinal medicine department)	Approximately 150 medical institutions
Hematology department	Approximately 10 medical institutions

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Request to and contract with the medical institutions will be conducted using web-based electronic data collection system (CCI [redacted]). The Medical Representative of PPD [redacted] will explain objectives and details of this survey, procedure, electronic signature, and handling of user ID and password of CCI [redacted] to the surveillance investigator based on "Implementation guidance", "Data entry screens of CCI [redacted]" and "CCI [redacted] operational manual" when this survey is requested. Thereafter, written contract is made with the medical institution and conduct of the survey will be requested within the prespecified duration of the survey.

7.3 Method of patient enrollment

Patients will be enrolled with "central enrollment method" using CCI [redacted] The surveillance investigator will enter the information required for patient enrollment (see Section 9.1) and will provide his/her electronic signature in CCI [redacted] concerning patients to whom drugs of triple therapy (three drugs including Takecab Tablets) are prescribed within 5 days after prescription day of the three drugs including Takecab Tablets (the prescription day is defined as "Day 0", and the day after prescription as "Day 1") after term of contract with the medical institution is started.

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

The surveillance investigator will enter the information of patient demographics and treatment and will provide electronic signature in CCI [redacted] for all patients enrolled in this survey by one month after completion of the observational period of each patient. If receipt of Takecab Tablets was not confirmed, it will be entered so in CCI [redacted] (it is not required to enter other data).

For the patients who discontinued triple therapy including Takecab Tablets for any reason during the observational period, the surveillance investigator will enter the information of patient demographics and treatment and will provide his/her electronic signature in CCI [redacted] by one month after completion of required observation. However, for patients who discontinued triple therapy including Takecab Tablets due to development of an AE, observation will be continued as much as possible until resolve or resolving from the AE even after the treatment is discontinued, and the observation results will be entered in CCI [redacted] with his/her electronic signature.

7.5 Actions to take at the time of development of a serious adverse event

The surveillance investigator will immediately communicate PPD [redacted] on development of a serious adverse event during the observational period. In addition, the surveillance investigator will provide detailed information separately if requested by PPD [redacted]

8.0 Scheduled period of the survey

Duration of the survey: September 2015 to April 30, 2017

Patient enrollment period: September 2015 to February 28, 2017 Note)

Note) Patients will not be enrolled in this survey (or entered in CCI) on or after March 1, 2017 even if Takecab Tablets is prescribed on or before February 28, 2017.
If enrollment of the planned number of patients of this survey is completed prior to February 28, 2017, the patient enrollment will be discontinued prior to the end of the patient enrollment period. When the patient enrollment period is shortened, the duration of the survey is to be changed according to the shortened period.

9.0 Data to be collected

The surveillance investigator will enter the information of the following items in CCI .
The schedule of this survey is presented in the Appendix.

9.1 Patient enrollment

1) Data to be collected

Prescription date of the three drugs including Takecab Tablets used in the triple therapy; patient identification number; patient initials; sex; date of birth; target disease of *H. pylori* eradication; assessment of inclusion and exclusion criteria

2) Data collection period

At the time of patient enrollment

9.2 Patient demographic information

1) Data to be collected

Inpatient/outpatient classification (at the time when triple therapy is started); predisposition of hypersensitivity (presence/absence and details); complication (presence/absence and details); details of previous *H. pylori* eradication (in patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor with amoxicillin and clarithromycin); height; weight; smoking history; drinking history; diagnosis of *H. pylori* infection (time of diagnosis and testing method)

2) Data collection period

At the start of triple therapy

9.3 Information of treatment

1) Data to be collected

Treatment compliance to Takecab Tablets and antimicrobials used for triple therapy (name of drugs; daily dose; duration of triple therapy and reason for discontinuation of the triple therapy); treatment compliance to concomitant drugs (excluding antimicrobials used for the triple therapy) (presence/absence; drug name(s), and indication(s))

2) Data collection period

Duration from the start to the completion (or the discontinuation) of triple therapy

9.4 Test/examination items

9.4.1 Determination of *H. pylori* eradication

1) Test items

Conduct of tests (presence/absence; reason if test is not conducted; testing method; date and result of determination)

2) Testing period

At the time of determination of *H. pylori* eradication*

* Time frame of the *H. pylori* determination is approximately from 4 weeks to 2 months after the triple therapy.

9.4.2 Liver function test

1) Test items

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

2) Testing period

Duration from the start of triple therapy* to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

* Within 1 month before starting triple therapy

9.4.3 Other examination items

1) Examination items

Presence/absence of pregnancy during the observational period (only female patients)

If pregnancy is confirmed during the observational period, the information is immediately communicated to PPD. The surveillance investigator provides detailed information (including information until delivery, e.g., pregnancy outcome such as premature delivery, as much as possible) separately when PPD requests it.

2) Examination period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

9.5 Adverse event

1) Data to be collected

Presence/absence of adverse event (AE) (See Table 1); AE term; onset date; seriousness and reason for seriousness (See Table 2); cause of discontinuation of triple therapy; outcome date; outcome; causality* with triple therapy (See Table 3)

Follow-up survey will be conducted as much as possible when outcome is not resolved or unknown and causality is determined as unassessable.

Detailed information (e.g., clinical course and results of tests conducted for diagnosis) will be collected as much as possible when onset of hepatic function disorder or gastrointestinal infection of clostridium difficile is observed.

* Following information will be collected: rationale of assessment when causality is assessed as not related, and reason when causality is determined as unassessable.

Note) A point to consider concerning adverse events

Abnormal exacerbation of the target disease, i.e., exacerbation worse than the expected natural course of the disease, will be handled as an adverse event.

2) Data collection period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

Table 1 Definition of adverse event

Adverse event (AE) is any unfavorable medical occurrence in a patient administered a pharmaceutical product. It does not necessarily need to have a causal relationship with the pharmaceutical product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory values), symptom, or disease occurring at the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Following cases should also be handled as adverse events. • Symptoms developed in an infant breastfed by a mother receiving the pharmaceutical product • Unfavorable symptoms, etc. developed in a child after administration of the pharmaceutical product • Symptoms developed after occupational exposure to the pharmaceutical product • Symptoms developed due to the use of a counterfeit of a pharmaceutical product manufactured/marketed by Takeda Pharmaceutical Company Limited • Unfavorable symptoms developed in a user of the pharmaceutical product which information was obtained through litigation or other legal actions

Table 2 Seriousness assessment criteria

An event meeting any of the following criteria is assessed as "serious":

1. Fatal (death)
2. Life-threatening (life-threatening)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Congenital anomaly/birth defect (congenital anomaly)
6. Other medically important condition than 1-5. Events listed in "Takeda Medically Significant AE List" are included in this criterion.

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/Acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes/Ventricular fibrillation/Ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Neuroleptic malignant syndrome/hyperthermia malignant
- Aplastic anaemia
- Abortion spontaneous/stillbirth and dead foetus
- Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Transmission or suspected transmission of infection via a medicinal product
- Hepatic necrosis
- Endotoxic shock or suspected endotoxic shock
- Acute hepatic failure

Table 3 Causality assessment criteria for adverse events and triple therapy

Assessment	Assessment criteria
Related	There is temporal relationship (including the clinical course after the discontinuation of the triple therapy). Or, while other factors such as underlying disease, complication, concomitant drug or concomitant procedure could be presumed, the AE is possibly related to triple therapy.
Not related	There is no temporal relationship with the triple therapy. Or, other factors such as underlying disease, complication, concomitant drug or concomitant procedure are quite considerable as the cause.
Unassessable	Information required for causality assessment, such as temporal relationship (including the clinical course after the discontinuation of the triple therapy), underlying disease, complication, concomitant drug, and concomitant procedure is insufficient.

10.0 Analysis items and method

10.1 Items related to patient disposition

Following data will be accumulated: number of patients enrolled; number of patients whose survey form (electronic) have been collected; number of patients in the safety analysis set and the efficacy analysis set; number of patients excluded from analysis and reasons for exclusion

10.2 Patient demographics

Patient demographic data including sex, age, hypersensitivity predisposition and complication will be accumulated.

10.3 Details of treatment

Treatment compliance to Takecab Tablets and antimicrobials used for the triple therapy and concomitant drugs (other than antimicrobials used for the triple therapy) will be accumulated.

10.4 Items related to safety

Following data will be accumulated for the safety analysis set. Adverse events are coded with MedDRA/J, and accumulated by Preferred Term (PT) and System Organ Class (SOC).
The patients enrolled to this survey in both first-line and second-line eradication cases will be accumulated separately.

10.4.1 Onset of adverse events

Frequencies of adverse events which developed during the observational period will be accumulated by type, onset period, seriousness, and causality with the triple therapy.

10.4.2 Factors which may affect safety

Frequencies of adverse reactions which developed during the observational period will be accumulated by subgroups of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; presence/absence of renal disorder complication; and presence/absence of liver disorder complication) and details of treatment (first-line and second-line eradication).

10.5 Items related to efficacy

Following data will be accumulated for the efficacy analysis set.

10.5.1 Eradication rate of *H. pylori*

In patients who have the result of determination of eradication, proportion of patients with *H. pylori* negative (eradication rate) will be accumulated by first-line and second-line eradication.

10.5.2 Factors which may affect efficacy

The eradication rates of *H. pylori* will be accumulated by subgroup of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; complication).

11.0 Registration of survey information

Takeda Pharmaceutical Company Limited will register information of this survey on the public websites before starting this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information

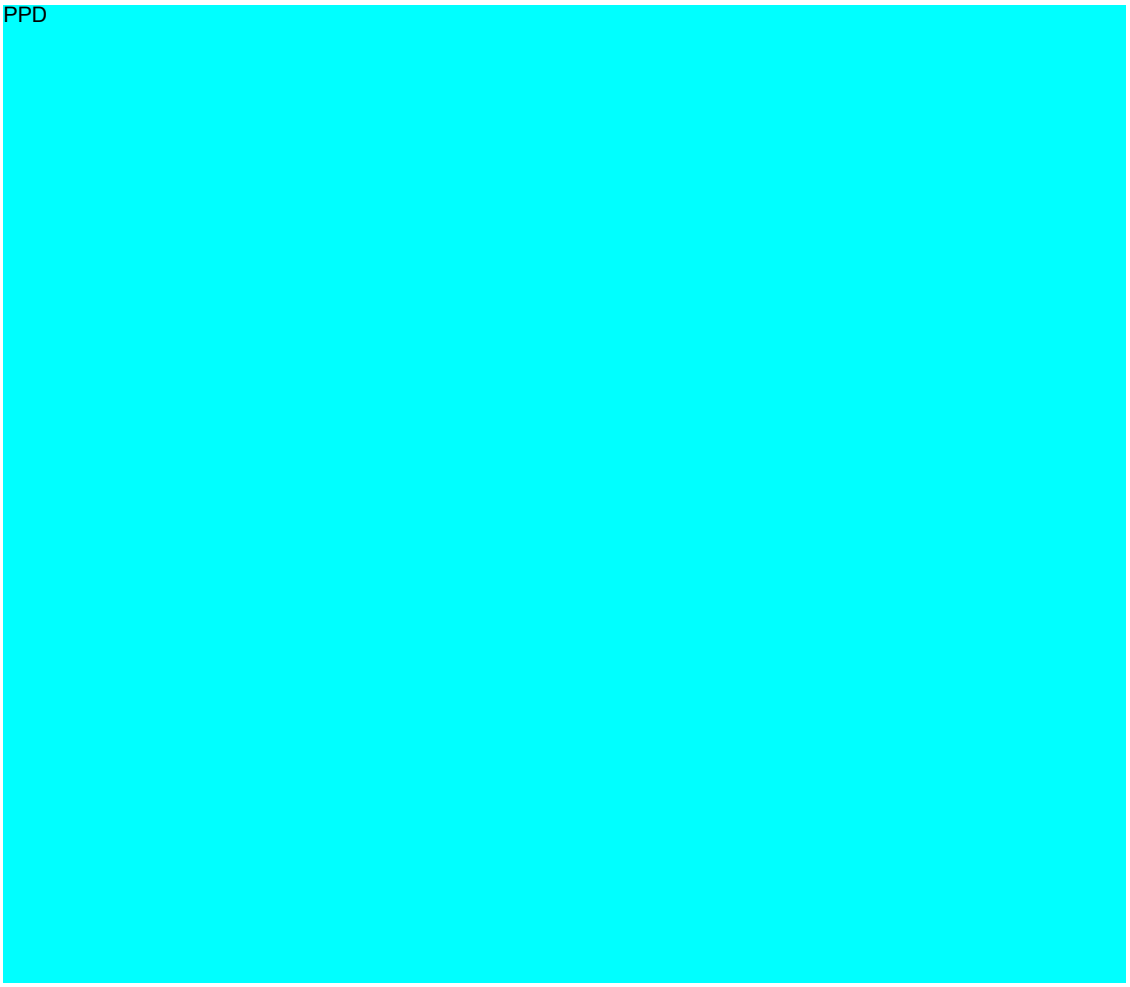
12.0 Organization of this survey

12.1 Manager

Takeda Pharmaceutical Company Limited

Post-marketing surveillance manager

13.0 Clinical research organizations



14.0 Other required items

14.1 Revision of the protocol

During the period of conducting this survey, following information will be captured: development of ADRs not expectable from Precautions for Use and onset of serious ADRs; whether there is increased frequency of specific ADRs or not; validity of the survey items. The protocol will be reviewed and revised if it is considered necessary. In addition, if a supplemental approval of a new dosage and administration or a new indication is granted

during the period of conducting this survey, necessity of revision of the protocol will be examined if needed, and the protocol will be revised if needed.

14.2 Procedure when there is any issue or doubt

If there is any safety or efficacy issue, data will be closely examined, and action will be considered.

Appendix: Observation schedule

Data to be collected \ Period of survey/data entry		Observational period				
		At the time of patient enrollment	At the start of triple therapy	At the completion of triple therapy	At the time of determination of *H. pylori* eradication Note 1)	At the time of discontinuation of triple therapy
Patient enrollment	Prescription date of 3 drugs including Takecab Tablets in triple therapy	○				
	Patient identification number	○				
	Patient initials	○				
	Sex	○				
	Date of birth	○				
	Target disease of *H. pylori* eradication	○				
	Assessment of inclusion criteria	○				
	Assessment of exclusion criteria	○				
Patient demographic information	Inpatient/outpatient classification		○			
	Hypersensitivity predisposition		○			
	Complication		○			
	Previous *H. pylori* eradication Note 2)		○			
	Height, weight		○			
	Smoking history		○			
	Drinking history		○			
	Diagnosis of *H. pylori* infection		○			
Information of treatment	Treatment compliance to Takecab Tablets and antimicrobials		←○→			○
	Treatment compliance to concomitant drugs (excluding antimicrobials)		←○→			○
Test/ examination items	Determination of *H. pylori* eradication				○	
	Liver function test		←○Note 3)→			○
	Presence/absence of pregnancy (only female patients)		←○→			○
	Adverse event		←○→			○

○ : To be conducted

←○→ : To be conducted throughout the period

Note 1) Approximately from 4 weeks to 2 months after the triple therapy is completed

Note 2) In patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor in combination with amoxicillin and clarithromycin

Note 3) From within one month before the start of triple therapy to determination of *H. pylori* eradication

Protocol of drug use surveillance

Drug use surveillance of Takecab tablets

"Supplement to *Helicobacter pylori* eradication"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vonoprazan-5002**
Version	**Version 3**
Date	**July 24, 2015**

Table of contents

1.0 Background of conduct

In the domestic clinical studies of *Helicobacter Pylori* (*H. pylori*) eradication with Takecab Tablets in combination with antimicrobials, safety of triple therapy was evaluated: Takecab Tablets, amoxicillin and clarithromycin (first-line eradication) in 329 patients, and Takecab Tablets, amoxicillin and metronidazole (second-line eradication) in 50 patients, and the results showed no specific issue.

The safety profile of the first-line eradication could be expected in view of the results of Takecab Tablets clinical studies in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis) and information provided in the package inserts of antimicrobials. Most of the adverse reactions (ADRs) developed during the second-line eradication were also observed in the first-line eradication, and there was no substantial difference between them. Accordingly, the safety profile of the use of Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.

The Drug use surveillance of Takecab Tablets (this survey) for the supplement to *H. pylori* eradication in first-line and second-line eradication in the routine clinical setting is planned to confirm validity of this estimation (whether there is a new safety concern or not).

This survey is conducted in compliance with relevant regulatory requirements such as GPSP ministerial ordinance.

2.0 Objectives

The objective of this survey is to evaluate the safety and efficacy of first-line and second-line eradication including Takecab Tablets (triple therapy) in the routine clinical setting.

3.0 Planned sample size and its rationale

3.1 Sample size

500 patients

3.2 Rationale

The safety profile of *H. pylori* eradication with a proton pump inhibitor (lansoprazole) in combination with antimicrobials (amoxicillin and clarithromycin) observed in the domestic clinical studies and the drug use surveillance could be expected from the results of the domestic clinical studies and the drug use surveillance of lansoprazole in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis), and from the information provided in the package inserts of antimicrobials.

The safety profile of the first-line eradication observed in the clinical studies for *H. pylori* eradication with Takecab Tablets in combination with antimicrobials could be expected from

the results of the clinical studies of Takecab Tablets in patients with acid-related diseases and information provided in the package inserts of antimicrobials.
Based on the above, the safety profile of the first-line eradication with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.
In addition, it has been confirmed that ADRs of *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and metronidazole) in the specific drug use surveillance of proton pump inhibitors (lansoprazole, omeprazole and rabeprazole) were mostly similar to the ADRs reported in *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and clarithromycin). Most of the ADRs developed during the second-line *H. pylori* eradication in the clinical study of Takecab Tablets in combination with antimicrobials were also observed in the first-line eradication. Therefore, it is estimated that ADRs developed in association with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication are not substantially different between first-line eradication and second-line eradication. In view of the above, the drug use surveillance of Takecab Tablets for supplement of *H. pylori* eradication is to be conducted for both first-line and second-line eradication.
Accordingly, in this survey, data will be collected from 500 patients to whom Takecab Tablets is administered for supplement of *H. pylori* eradication, and will be compared with the safety information of Takecab Tablets collected in the drug use surveillance in patients with acid-related diseases (total 3,000 patients) and with information provided in the package inserts of antimicrobials, and it will be confirmed whether there is a new safety concern or not (please note that the sample size of 500 patients is not statistically calculated).
In this survey, patients excluded from the clinical studies such as with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis will be enrolled.

4.0 Study population

Patients with the diseases described below* will receive triple therapy for *H. pylori* eradication. However, patients should meet the inclusion criterion and should not meet the exclusion criterion described below. Refer to the Precautions section of the package insert.

* If a patient's first-line eradication is unsuccessful in this survey, the patient can be enrolled in the second-line eradication in this survey.

Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis

4.1 Inclusion criteria

Patients who meet either of the following criteria will be included in the survey:

[1] Patients receiving *H. pylori* eradication for the first time

[2] Patients for whom *H. pylori* eradication with Takecab Tablets or proton pump inhibitor + amoxicillin + clarithromycin was found unsuccessful and who are to receive eradication treatment with amoxicillin and metronidazole

4.2 Exclusion criteria

Patients who meet either of the following criteria will not be included in the survey. Refer to the Contraindications and Precautions section of the package insert of antimicrobials used in the triple therapy.

[1] Patients with previous history of hypersensitivity to ingredients in Takecab Tablets

[2] Patients receiving atazanavir sulfate or rilpivirine hydrochloride

5.0 Dosage and administration

The usual dose for adults is 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. These three drugs will be orally administered at the same time, twice daily for 7 days. The dose of clarithromycin can be increased as clinically warranted. However, the dosage of clarithromycin should not exceed 400 mg (potency)/dose twice daily.

If *H. pylori* eradication with a three-drug regimen comprising vonoprazan or proton pump inhibitor + amoxicillin hydrate + clarithromycin is unsuccessful, as an alternative treatment, the following three drugs will be orally administered to adults at the same time, twice daily for 7 days: vonoprazan at a dose of 20 mg, amoxicillin hydrate at a dose of 750 mg (potency), and metronidazole at a dose of 250 mg. Refer to the Precautions section of the package insert of antimicrobials used in triple therapy.

6.0 Number of medical institutions by departments where the survey is planned

Internal medicine department (such as gastrointestinal medicine department)	Approximately 150 medical institutions
Hematology department	Approximately 10 medical institutions

7.0 Method

7.1 Observational period

Triple therapy period (7 days) and the period from the completion of the triple therapy to the determination of *H. pylori* eradication

Time frame of the *H. pylori* determination is approximately from 4 weeks* to 2 months after the triple therapy.

* According to the "Guidelines for diagnosis and treatment of *H. pylori* infection" of the Japanese Society for *Helicobacter* Research, determination of *H. pylori* eradication should be conducted after 4 weeks

from discontinuation of eradication therapy.

7.2 Request to and contract with the medical institutions

Request to and contract with the medical institutions will be conducted using web-based electronic data collection system (CCI). The Medical Representative of PPD will explain objectives and details of this survey, procedure, electronic signature, and handling of user ID and password of CCI to the surveillance investigator based on “Implementation guidance”, “Data entry screens of CCI ” and “CCI operational manual” when this survey is requested. Thereafter, written contract is made with the medical institution and conduct of the survey will be requested within the prespecified duration of the survey.

7.3 Method of patient enrollment

Patients will be enrolled with “central enrollment method” using CCI . The surveillance investigator will enter the information required for patient enrollment (see Section 9.1) and will provide his/her electronic signature in CCI concerning patients to whom drugs of triple therapy (three drugs including Takecab Tablets) are prescribed within 5 days after prescription day of the three drugs including Takecab Tablets (the prescription day is defined as “Day 0”, and the day after prescription as “Day 1”) after term of contract with the medical institution is started.

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

The surveillance investigator will enter the information of patient demographics and treatment and will provide electronic signature in CCI for all patients enrolled in this survey by one month after completion of the observational period of each patient. If receipt of Takecab Tablets was not confirmed, it will be entered so in CCI (it is not required to enter other data).

For the patients who discontinued triple therapy including Takecab Tablets for any reason during the observational period, the surveillance investigator will enter the information of patient demographics and treatment and will provide his/her electronic signature in CCI by one month after completion of required observation. However, for patients who discontinued triple therapy including Takecab Tablets due to development of an AE, observation will be continued as much as possible until resolve or resolving from the AE even after the treatment is discontinued, and the observation results will be entered in CCI with his/her electronic signature.

7.5 Actions to take at the time of development of a serious adverse event

The surveillance investigator will immediately communicate PPD on development of a serious adverse event during the observational period. In addition, the surveillance investigator will provide detailed information separately if requested by PPD .

8.0 Scheduled period of the survey

Duration of the survey: September 2015 to April 30, 2017

Patient enrollment period: September 2015 to February 28, 2017 Note)

Note) Patients will not be enrolled in this survey (or entered in CCI) on or after March 1, 2017 even if Takecab Tablets is prescribed on or before February 28, 2017.
If enrollment of the planned number of patients of this survey is completed prior to February 28, 2017, the patient enrollment will be discontinued prior to the end of the patient enrollment period. When the patient enrollment period is shortened, the duration of the survey is to be changed according to the shortened period.

9.0 Data to be collected

The surveillance investigator will enter the information of the following items in CCI
The schedule of this survey is presented in the Appendix.

9.1 Patient enrollment

1) Data to be collected

Prescription date of the three drugs including Takecab Tablets used in the triple therapy; patient identification number; patient initials; sex; date of birth; target disease of *H. pylori* eradication; assessment of inclusion and exclusion criteria

2) Data collection period

At the time of patient enrollment

9.2 Patient demographic information

1) Data to be collected

Inpatient/outpatient classification (at the time when triple therapy is started); predisposition of hypersensitivity (presence/absence and details); complication (presence/absence and details); details of previous *H. pylori* eradication (in patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor with amoxicillin and clarithromycin); height; weight; smoking history; drinking history; diagnosis of *H. pylori* infection (time of diagnosis and testing method)

2) Data collection period

At the start of triple therapy

9.3 Information of treatment

1) Data to be collected

Treatment compliance to Takecab Tablets and antimicrobials used for triple therapy (name of drugs; daily dose; duration of triple therapy and reason for discontinuation of the triple therapy); treatment compliance to concomitant drugs (excluding antimicrobials used for the triple therapy) (presence/absence; drug name(s), and indication(s))

2) Data collection period

Duration from the start to the completion (or the discontinuation) of triple therapy

9.4 Test/examination items

9.4.1 Determination of *H. pylori* eradication

1) Test items

Conduct of tests (presence/absence; reason if test is not conducted; testing method; date and result of determination)

2) Testing period

At the time of determination of *H. pylori* eradication*

* Time frame of the *H. pylori* determination is approximately from 4 weeks to 2 months after the triple therapy.

9.4.2 Liver function test

1) Test items

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

2) Testing period

Duration from the start of triple therapy* to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

* Within 1 month before starting triple therapy

9.4.3 Other examination items

1) Examination items

Presence/absence of pregnancy during the observational period (only female patients)
If pregnancy is confirmed during the observational period, the information is immediately communicated to PPD The surveillance investigator provides detailed information (including information until delivery, e.g., pregnancy outcome such as premature delivery, as much as possible) separately when PPD requests it.

2) Examination period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

9.5 Adverse event

1) Data to be collected

Presence/absence of adverse event (AE) (See Table 1); AE term; onset date; seriousness and reason for seriousness (See Table 2); cause of discontinuation of triple therapy; outcome date; outcome; causality* with triple therapy (See Table 3)
Follow-up survey will be conducted as much as possible when outcome is not resolved or unknown and causality is determined as unassessable.

Detailed information (e.g., clinical course, and results of tests conducted for diagnosis) will be collected as much as possible when onset of hepatic function disorder or gastrointestinal infection of clostridium difficile is observed.

* Following information will be collected: rationale of assessment when causality is assessed as not related, and reason when causality is determined as unassessable.

Note) A point to consider concerning adverse events

Abnormal exacerbation of the target disease, i.e., exacerbation worse than the expected natural course of the disease, will be handled as an adverse event.

2) Data collection period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

Table 1 Definition of adverse event

Adverse event (AE) is any unfavorable medical occurrence in a patient administered a pharmaceutical product. It does not necessarily need to have a causal relationship with the pharmaceutical product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory values), symptom, or disease occurring at the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Following cases should also be handled as adverse events. • Symptoms developed in an infant breastfed by a mother receiving the pharmaceutical product • Unfavorable symptoms, etc. developed in a child after administration of the pharmaceutical product • Symptoms developed after occupational exposure to the pharmaceutical product • Symptoms developed due to the use of a counterfeit of a pharmaceutical product manufactured/marketed by Takeda Pharmaceutical Company Limited • Unfavorable symptoms developed in a user of the pharmaceutical product which information was obtained through litigation or other legal actions

Table 2 Seriousness assessment criteria

An event meeting any of the following criteria is assessed as "serious":

1. Fatal (death)
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3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Congenital anomaly/birth defect (congenital anomaly)
6. Other medically important condition than 1-5. Events listed in "Takeda Medically Significant AE List" are included in this criterion.

<u>Takeda Medically Significant AE List</u>

- Acute respiratory failure/Acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes/Ventricular fibrillation/Ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Neuroleptic malignant syndrome/hyperthermia malignant
- Aplastic anaemia
- Abortion spontaneous/stillbirth and dead foetus
- Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Transmission or suspected transmission of infection via a medicinal product
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- Acute hepatic failure

Table 3 Causality assessment criteria for adverse events and triple therapy

Assessment	Assessment criteria
Related	There is temporal relationship (including the clinical course after the discontinuation of the triple therapy). Or, while other factors such as underlying disease, complication, concomitant drug or concomitant procedure could be presumed, the AE is possibly related to triple therapy.
Not related	There is no temporal relationship with the triple therapy. Or, other factors such as underlying disease, complication, concomitant drug or concomitant procedure are quite considerable as the cause.
Unassessable	Information required for causality assessment, such as temporal relationship (including the clinical course after the discontinuation of the triple therapy), underlying disease, complication, concomitant drug, and concomitant procedure is insufficient.

10.0 Analysis items and method

10.1 Items related to patient disposition

Following data will be accumulated: number of patients enrolled; number of patients whose survey form (electronic) have been collected; number of patients in the safety analysis set and the efficacy analysis set; number of patients excluded from analysis and reasons for exclusion

10.2 Patient demographics

Patient demographic data including sex, age, hypersensitivity predisposition and complication will be accumulated.

10.3 Details of treatment

Treatment compliance to Takecab Tablets and antimicrobials used for the triple therapy and concomitant drugs (other than antimicrobials used for the triple therapy) will be accumulated.

10.4 Items related to safety

Following data will be accumulated for the safety analysis set. Adverse events are coded with MedDRA/J, and accumulated by Preferred Term (PT) and System Organ Class (SOC).
The patients enrolled to this survey in both first-line and second-line eradication cases will be accumulated separately.

10.4.1 Onset of adverse events

Frequencies of adverse events which developed during the observational period will be accumulated by type, onset period, seriousness, and causality with the triple therapy.

10.4.2 Factors which may affect safety

Frequencies of adverse reactions which developed during the observational period will be accumulated by subgroups of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; presence/absence of renal disorder complication; and presence/absence of liver disorder complication) and details of treatment (first-line and second-line eradication).

10.5 Items related to efficacy

Following data will be accumulated for the efficacy analysis set.

10.5.1 Eradication rate of *H. pylori*

In patients who have the result of determination of eradication, proportion of patients with *H. pylori* negative (eradication rate) will be accumulated by first-line and second-line eradication.

10.5.2 Factors which may affect efficacy

The eradication rates of *H. pylori* will be accumulated by subgroup of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; complication).

11.0 Registration of survey information

Takeda Pharmaceutical Company Limited will register information of this survey on the public websites before starting this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organization of this survey

12.1 Manager

Takeda Pharmaceutical Company Limited

Post-marketing surveillance manager

13.0 Clinical research organizations

PPD

14.0 Other required items

14.1 Revision of the protocol

During the period of conducting this survey, following information will be captured: development of ADRs not expectable from Precautions for Use and onset of serious ADRs; whether there is increased frequency of specific ADRs or not; validity of the survey items. The protocol will be reviewed and revised if it is considered necessary. In addition, if a supplemental approval of a new dosage and administration or a new indication is granted during the period of conducting this survey, necessity of revision of the protocol will be examined if needed, and the protocol will be revised if needed.

14.2 Procedure when there is any issue or doubt

If there is any safety or efficacy issue, data will be closely examined, and action will be considered.

Appendix: Observation schedule

Data to be collected \ Period of survey/data entry		Observational period				
		At the time of patient enrollment	At the start of triple therapy	At the completion of triple therapy	At the time of determination of *H. pylori* eradication Note 1)	At the time of discontinuation of triple therapy
Patient enrollment	Prescription date of 3 drugs including Takecab Tablets in triple therapy	○				
	Patient identification number	○				
	Patient initials	○				
	Sex	○				
	Date of birth	○				
	Target disease of *H. pylori* eradication	○				
	Assessment of inclusion criteria	○				
	Assessment of exclusion criteria	○				
Patient demographic information	Inpatient/outpatient classification		○			
	Hypersensitivity predisposition		○			
	Complication		○			
	Previous *H. pylori* eradication Note 2)		○			
	Height, weight		○			
	Smoking history		○			
	Drinking history		○			
	Diagnosis of *H. pylori* infection		○			
Information of treatment	Treatment compliance to Takecab Tablets and antimicrobials		←○→			○
	Treatment compliance to concomitant drugs (excluding antimicrobials)		←○→			○
Test/ examination items	Determination of *H. pylori* eradication				○	
	Liver function test		←○Note 3)→			○
	Presence/absence of pregnancy (only female patients)		←○→			○
	Adverse event		←○→			○

○ : To be conducted

←○→ : To be conducted throughout the period

Note 1) Approximately from 4 weeks to 2 months after the triple therapy is completed

Note 2) In patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor in combination with amoxicillin and clarithromycin

Note 3) From within one month before the start of triple therapy to determination of *H. pylori* eradication

Protocol of drug use surveillance

Drug use surveillance of Takecab tablets

"Supplement to *Helicobacter pylori* eradication"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vonoprazan-5002**
Version	**Version 2**
Date	**June 22, 2015**

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1.0 Background of conduct

In the domestic clinical studies of *Helicobacter Pylori* (*H. pylori*) eradication with Takecab Tablets in combination with antimicrobials, safety of triple therapy was evaluated: Takecab Tablets, amoxicillin and clarithromycin (first-line eradication) in 329 patients, and Takecab Tablets, amoxicillin and metronidazole (second-line eradication) in 50 patients, and the results showed no specific issue.

The safety profile of the first-line eradication could be expected in view of the results of Takecab Tablets clinical studies in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis) and information provided in the package inserts of antimicrobials. Most of the adverse reactions (ADRs) developed during the second-line eradication were also observed in the first-line eradication, and there was no substantial difference between them. Accordingly, the safety profile of the use of Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.

The Drug use surveillance of Takecab Tablets (this survey) for the supplement to *H. pylori* eradication in first-line and second-line eradication in the routine clinical setting is planned to confirm validity of this estimation (whether there is a new safety concern or not).

This survey is conducted in compliance with relevant regulatory requirements such as GPSP ministerial ordinance.

2.0 Objectives

The objective of this survey is to evaluate the safety and efficacy of first-line and second-line eradication including Takecab Tablets (triple therapy) in the routine clinical setting.

3.0 Planned sample size and its rationale

3.1 Sample size

500 patients

3.2 Rationale

The safety profile of *H. pylori* eradication with a proton pump inhibitor (lansoprazole) in combination with antimicrobials (amoxicillin and clarithromycin) observed in the domestic clinical studies and the drug use surveillance could be expected from the results of the domestic clinical studies and the drug use surveillance of lansoprazole in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis), and from the information provided in the package inserts of antimicrobials.

The safety profile of the first-line eradication observed in the clinical studies for *H. pylori* eradication with Takecab Tablets in combination with antimicrobials could be expected from

the results of the clinical studies of Takecab Tablets in patients with acid-related diseases and information provided in the package inserts of antimicrobials.
Based on the above, the safety profile of the first-line eradication with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.
In addition, it has been confirmed that ADRs of *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and metronidazole) in the specific drug use surveillance of proton pump inhibitors (lansoprazole, omeprazole and rabeprazole) were mostly similar to the ADRs reported in *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and clarithromycin). Most of the ADRs developed during the second-line *H. pylori* eradication in the clinical study of Takecab Tablets in combination with antimicrobials were also observed in the first-line eradication. Therefore, it is estimated that ADRs developed in association with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication are not substantially different between first-line eradication and second-line eradication. In view of the above, the drug use surveillance of Takecab Tablets for supplement of *H. pylori* eradication is to be conducted for both first-line and second-line eradication.
Accordingly, in this survey, data will be collected from 500 patients to whom Takecab Tablets is administered for supplement of *H. pylori* eradication, and will be compared with the safety information of Takecab Tablets collected in the drug use surveillance in patients with acid-related diseases (total 3,000 patients) and with information provided in the package inserts of antimicrobials, and it will be confirmed whether there is a new safety concern or not (please note that the sample size of 500 patients is not statistically calculated).
In this survey, patients excluded from the clinical studies such as with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis will be enrolled.

4.0 Study population

Patients with the diseases described below* will receive triple therapy for *H. pylori* eradication. However, patients should meet the inclusion criterion and should not meet the exclusion criterion described below. Refer to the Precautions section of the package insert.

* If a patient's first-line eradication is unsuccessful in this survey, the patient can be enrolled in the second-line eradication in this survey.

Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis

4.1 Inclusion criteria

Patients who meet either of the following criteria will be included in the survey:

[1] Patients receiving *H. pylori* eradication for the first time

[2] Patients for whom *H. pylori* eradication with Takecab Tablets or proton pump inhibitor + amoxicillin + clarithromycin was found unsuccessful and who are to receive eradication treatment with amoxicillin and metronidazole

4.2 Exclusion criteria

Patients who meet either of the following criteria will not be included in the survey. Refer to the Contraindications and Precautions section of the package insert of antimicrobials used in the triple therapy.

[1] Patients with previous history of hypersensitivity to ingredients in Takecab Tablets

[2] Patients receiving atazanavir sulfate or rilpivirine hydrochloride

5.0 Dosage and administration

The usual dose for adults is 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. These three drugs will be orally administered at the same time, twice daily for 7 days. The dose of clarithromycin can be increased as clinically warranted. However, the dosage of clarithromycin should not exceed 400 mg (potency)/dose twice daily.

If *H. pylori* eradication with a three-drug regimen comprising vonoprazan or proton pump inhibitor + amoxicillin hydrate + clarithromycin is unsuccessful, as an alternative treatment, the following three drugs will be orally administered to adults at the same time, twice daily for 7 days: vonoprazan at a dose of 20 mg, amoxicillin hydrate at a dose of 750 mg (potency), and metronidazole at a dose of 250 mg. Refer to the Precautions section of the package insert of antimicrobials used in triple therapy.

6.0 Number of medical institutions by departments where the survey is planned

Internal medicine department (such as gastrointestinal medicine department)	Approximately 150 medical institutions
Hematology department	Approximately 10 medical institutions

7.0 Method

7.1 Observational period

Triple therapy period (7 days) and the period from the completion of the triple therapy to the determination of *H. pylori* eradication

Time frame of the *H. pylori* determination is approximately from 4 weeks* to 2 months after the triple therapy.

* According to the "Guidelines for diagnosis and treatment of *H. pylori* infection" of the Japanese Society for *Helicobacter* Research, determination of *H. pylori* eradication should be conducted after 4 weeks

from discontinuation of eradication therapy.

7.2 Request to and contract with the medical institutions

Request to and contract with the medical institutions will be conducted using web-based electronic data collection system (CCI). The Medical Representative of PPD will explain objectives and details of this survey, procedure, electronic signature, and handling of user ID and password of CCI to the surveillance investigator based on “Implementation guidance”, “Data entry screens of CCI ” and “CCI operational manual” when this survey is requested. Thereafter, written contract is made with the medical institution and conduct of the survey will be requested within the prespecified duration of the survey.

7.3 Method of patient enrollment

Patients will be enrolled with “central enrollment method” using CCI . The surveillance investigator will enter the information required for patient enrollment (see Section 9.1) and will provide his/her electronic signature in CCI concerning patients to whom drugs of triple therapy (three drugs including Takecab Tablets) are prescribed within 5 days after prescription day of the three drugs including Takecab Tablets (the prescription day is defined as “Day 0”, and the day after prescription as “Day 1”) after term of contract with the medical institution is started.

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

The surveillance investigator will enter the information of patient demographics and treatment and will provide electronic signature in CCI for all patients enrolled in this survey by one month after completion of the observational period of each patient. If receipt of Takecab Tablets was not confirmed, it will be entered so in CCI (it is not required to enter other data).

For the patients who discontinued triple therapy including Takecab Tablets for any reason during the observational period, the surveillance investigator will enter the information of patient demographics and treatment and will provide his/her electronic signature in CCI by one month after completion of required observation. However, for patients who discontinued triple therapy including Takecab Tablets due to development of an AE, observation will be continued as much as possible until resolve or resolving from the AE even after the treatment is discontinued, and the observation results will be entered in CCI with his/her electronic signature.

7.5 Actions to take at the time of development of a serious adverse event

The surveillance investigator will immediately communicate PPD on development of a serious adverse event during the observational period. In addition, the surveillance investigator will provide detailed information separately if requested by PPD .

8.0 Scheduled period of the survey

Duration of the survey: September 2015 to April 30, 2017

Patient enrollment period: September 2015 to February 28, 2017 Note)

Note) Patients will not be enrolled in this survey (or entered in CCI) on or after March 1, 2017 even if Takecab Tablets is prescribed on or before February 28, 2017.

If enrollment of the planned number of patients of this survey is completed prior to February 28, 2017, the patient enrollment will be discontinued prior to the end of the patient enrollment period. When the patient enrollment period is shortened, the duration of the survey is to be changed according to the shortened period.

9.0 Data to be collected

The surveillance investigator will enter the information of the following items in CCI . The schedule of this survey is presented in the Appendix.

9.1 Patient enrollment

1) Data to be collected

Prescription date of the three drugs including Takecab Tablets used in the triple therapy; patient identification number; patient initials; sex; date of birth; target disease of *H. pylori* eradication; assessment of inclusion and exclusion criteria

2) Data collection period

At the time of patient enrollment

9.2 Patient demographic information

1) Data to be collected

Inpatient/outpatient classification (at the time when triple therapy is started); predisposition of hypersensitivity (presence/absence and details); complication (presence/absence and details); details of previous *H. pylori* eradication (in patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor with amoxicillin and clarithromycin); height; weight; smoking history; drinking history; diagnosis of *H. pylori* infection (time of diagnosis and testing method)

2) Data collection period

At the start of triple therapy

9.3 Information of treatment

1) Data to be collected

Treatment compliance to Takecab Tablets and antimicrobials used for triple therapy (name of drugs; daily dose; duration of triple therapy and reason for discontinuation of the triple therapy); treatment compliance to concomitant drugs (excluding antimicrobials used for the triple therapy) (presence/absence; drug name(s), and indication(s))

2) Data collection period

Duration from the start to the completion (or the discontinuation) of triple therapy

9.4 Test/examination items

9.4.1 Determination of *H. pylori* eradication

1) Test items

Conduct of tests (presence/absence; reason if test is not conducted; testing method; date and result of determination)

2) Testing period

At the time of determination of *H. pylori* eradication*

* Time frame of the *H. pylori* determination is approximately from 4 weeks to 2 months after the triple therapy.

9.4.2 Liver function test

1) Test items

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

2) Testing period

Duration from the start of triple therapy* to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

* Within 1 month before starting triple therapy

9.4.3 Other examination items

1) Examination items

Presence/absence of pregnancy during the observational period (only female patients)
If pregnancy is confirmed during the observational period, the information is immediately communicated to PPD The surveillance investigator provides detailed information (including information until delivery, e.g., pregnancy outcome such as premature delivery, as much as possible) separately when PPD requests it.

2) Examination period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

9.5 Adverse event

1) Data to be collected

Presence/absence of adverse event (AE) (See Table 1); AE term; onset date; seriousness and reason for seriousness (See Table 2); cause of discontinuation of triple therapy; outcome date; outcome; causality* with triple therapy (See Table 3)
Follow-up survey will be conducted as much as possible when outcome is not resolved or unknown and causality is determined as unassessable.

Detailed information (e.g., clinical course and results of tests conducted for diagnosis) will be collected as much as possible when onset of hepatic function disorder or gastrointestinal infection of clostridium difficile is observed.

* Following information will be collected: rationale of assessment when causality is assessed as not related, and reason when causality is determined as unassessable.

Note) A point to consider concerning adverse events

Abnormal exacerbation of the target disease, i.e., exacerbation worse than the expected natural course of the disease will be handled as an adverse event, but expected exacerbation of the target disease will not be handled as an adverse event.

2) Data collection period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

Table 1 Definition of adverse event

Adverse event (AE) is any unfavorable medical occurrence in a patient administered a pharmaceutical product. It does not necessarily need to have a causal relationship with the pharmaceutical product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory values), symptom, or disease occurring at the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Following cases should also be handled as adverse events. • Symptoms developed in an infant breastfed by a mother receiving the pharmaceutical product • Unfavorable symptoms, etc. developed in a child after administration of the pharmaceutical product • Symptoms developed after occupational exposure to the pharmaceutical product • Symptoms developed due to the use of a counterfeit of a pharmaceutical product manufactured/marketed by Takeda Pharmaceutical Company Limited • Unfavorable symptoms developed in a user of the pharmaceutical product which information was obtained through litigation or other legal actions

Table 2 Seriousness assessment criteria

An event meeting any of the following criteria is assessed as "serious":

1. Fatal (death)
2. Life-threatening (life-threatening)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Congenital anomaly/birth defect (congenital anomaly)
6. Other medically important condition than 1-5. Events listed in "Takeda Medically Significant AE List" are included in this criterion.

Takeda Medically Significant AE List

- Acute respiratory failure/Acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes/Ventricular fibrillation/Ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Neuroleptic malignant syndrome/hyperthermia malignant
- Aplastic anaemia
- Abortion spontaneous/stillbirth and dead foetus
- Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Transmission or suspected transmission of infection via a medicinal product
- Hepatic necrosis
- Endotoxic shock or suspected endotoxic shock
- Acute hepatic failure

Table 3 Causality assessment criteria for adverse events and triple therapy

Assessment	Assessment criteria
Related	There is temporal relationship (including the clinical course after the discontinuation of the triple therapy). Or, while other factors such as underlying disease, complication, concomitant drug or concomitant procedure could be presumed, the AE is possibly related to triple therapy.
Not related	There is no temporal relationship with the triple therapy. Or, other factors such as underlying disease, complication, concomitant drug or concomitant procedure are quite considerable as the cause.
Unassessable	Information required for causality assessment, such as temporal relationship (including the clinical course after the discontinuation of the triple therapy), underlying disease, complication, concomitant drug, and concomitant procedure is insufficient.

10.0 Analysis items and method

10.1 Items related to patient disposition

Following data will be accumulated: number of patients enrolled; number of patients whose survey form (electronic) have been collected; number of patients in the safety analysis set and the efficacy analysis set; number of patients excluded from analysis and reasons for exclusion

10.2 Patient demographics

Patient demographic data including sex, age, hypersensitivity predisposition and complication will be accumulated.

10.3 Details of treatment

Treatment compliance to Takecab Tablets and antimicrobials used for the triple therapy and concomitant drugs (other than antimicrobials used for the triple therapy) will be accumulated.

10.4 Items related to safety

Following data will be accumulated for the safety analysis set. Adverse events are coded with MedDRA/J, and accumulated by Preferred Term (PT) and System Organ Class (SOC).
The patients enrolled to this survey in both first-line and second-line eradication cases will be accumulated separately.

10.4.1 Onset of adverse events

Frequencies of adverse events which developed during the observational period will be accumulated by type, onset period, seriousness, and causality with the triple therapy.

10.4.2 Factors which may affect safety

Frequencies of adverse reactions which developed during the observational period will be accumulated by subgroups of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; presence/absence of renal disorder complication; and presence/absence of liver disorder complication) and details of treatment (first-line and second-line eradication).

10.5 Items related to efficacy

Following data will be accumulated for the efficacy analysis set.

10.5.1 Eradication rate of *H. pylori*

In patients who have the result of determination of eradication, proportion of patients with *H. pylori* negative (eradication rate) will be accumulated by first-line and second-line eradication.

10.5.2 Factors which may affect efficacy

The eradication rates of *H. pylori* will be accumulated by subgroup of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; complication).

11.0 Registration of survey information

Takeda Pharmaceutical Company Limited will register information of this survey on the public websites before starting this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information

12.0 Organization of this survey

12.1 Manager

Takeda Pharmaceutical Company Limited

Post-marketing surveillance manager

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PPD

14.0 Other required items

14.1 Revision of the protocol

During the period of conducting this survey, following information will be captured: development of ADRs not expectable from Precautions for Use and onset of serious ADRs; whether there is increased frequency of specific ADRs or not; validity of the survey items. The protocol will be reviewed and revised if it is considered necessary. In addition, if a supplemental approval of a new dosage and administration or a new indication is granted during the period of conducting this survey, necessity of revision of the protocol will be examined if needed, and the protocol will be revised if needed.

14.2 Procedure when there is any issue or doubt

If there is any safety or efficacy issue, data will be closely examined, and action will be considered.

Appendix: Observation schedule

Data to be collected \ Period of survey/data entry		Observational period				
		At the time of patient enrollment	At the start of triple therapy	At the completion of triple therapy	At the time of determination of *H. pylori* eradication Note 1)	At the time of discontinuation of triple therapy
Patient enrollment	Prescription date of 3 drugs including Takecab Tablets in triple therapy	○				
	Patient identification number	○				
	Patient initials	○				
	Sex	○				
	Date of birth	○				
	Target disease of *H. pylori* eradication	○				
	Assessment of inclusion criteria	○				
	Assessment of exclusion criteria	○				
Patient demographic information	Inpatient/outpatient classification		○			
	Hypersensitivity predisposition		○			
	Complication		○			
	Previous *H. pylori* eradication Note 2)		○			
	Height, weight		○			
	Smoking history		○			
	Drinking history		○			
	Diagnosis of *H. pylori* infection		○			
Information of treatment	Treatment compliance to Takecab Tablets and antimicrobials		←○→			○
	Treatment compliance to concomitant drugs (excluding antimicrobials)		←○→			○
Test/ examination items	Determination of *H. pylori* eradication				○	
	Liver function test		←○Note 3)→			○
	Presence/absence of pregnancy (only female patients)		←○→			○
	Adverse event		←○→			○

○ : To be conducted

←○→ : To be conducted throughout the period

Note 1) Approximately from 4 weeks to 2 months after the triple therapy is completed

Note 2) In patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor in combination with amoxicillin and clarithromycin

Note 3) From within one month before the start of triple therapy to determination of *H. pylori* eradication

Protocol of drug use surveillance

Drug use surveillance of Takecab tablets

"Supplement to *Helicobacter pylori* eradication"

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vonoprazan-5002**
Version	**Version 1**
Date	**January 6, 2015**

Table of contents

1.0 Background of conduct

In the domestic clinical studies of *Helicobacter Pylori* (*H. pylori*) eradication with Takecab Tablets in combination with antimicrobials, safety of triple therapy was evaluated: Takecab Tablets, amoxicillin and clarithromycin (first-line eradication) in 329 patients, and Takecab Tablets, amoxicillin and metronidazole (second-line eradication) in 50 patients, and the results showed no specific issue.

The safety profile of the first-line eradication could be expected in view of the results of Takecab Tablets clinical studies in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis) and information provided in the package inserts of antimicrobials. Most of the adverse reactions (ADRs) developed during the second-line eradication were also observed in the first-line eradication, and there was no substantial difference between them. Accordingly, the safety profile of the use of Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.

The Drug use surveillance of Takecab Tablets (this survey) for the supplement to *H. pylori* eradication in first-line and second-line eradication in the routine clinical setting is planned to confirm validity of this estimation (whether there is a new safety concern or not).

This survey is conducted in compliance with relevant regulatory requirements such as GPSP ministerial ordinance.

2.0 Objectives

The objective of this survey is to evaluate the safety and efficacy of first-line and second-line eradication including Takecab Tablets (triple therapy) in the routine clinical setting.

3.0 Planned sample size and its rationale

3.1 Sample size

500 patients

3.2 Rationale

The safety profile of *H. pylori* eradication with a proton pump inhibitor (lansoprazole) in combination with antimicrobials (amoxicillin and clarithromycin) observed in the domestic clinical studies and the drug use surveillance could be expected from the results of the domestic clinical studies and the drug use surveillance of lansoprazole in patients with acid-related diseases (gastric ulcer, duodenal ulcer and reflux oesophagitis), and from the information provided in the package inserts of antimicrobials.

The safety profile of the first-line eradication observed in the clinical studies for *H. pylori* eradication with Takecab Tablets in combination with antimicrobials could be expected from

the results of the clinical studies of Takecab Tablets in patients with acid-related diseases and information provided in the package inserts of antimicrobials.
Based on the above, the safety profile of the first-line eradication with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication in the routine clinical setting can be estimated based on the safety profile to be confirmed in the drug use surveillance of Takecab Tablets in patients with acid-related diseases (3,000 patients) and information provided in the package inserts of antimicrobials.
In addition, it has been confirmed that ADRs of *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and metronidazole) in the specific drug use surveillance of proton pump inhibitors (lansoprazole, omeprazole and rabeprazole) were mostly similar to the ADRs reported in *H. pylori* eradication with a proton pump inhibitor in combination with antimicrobials (amoxicillin and clarithromycin). Most of the ADRs developed during the second-line *H. pylori* eradication in the clinical study of Takecab Tablets in combination with antimicrobials were also observed in the first-line eradication. Therefore, it is estimated that ADRs developed in association with Takecab Tablets in combination with antimicrobials for *H. pylori* eradication are not substantially different between first-line eradication and second-line eradication. In view of the above, the drug use surveillance of Takecab Tablets for supplement of *H. pylori* eradication is to be conducted for both first-line and second-line eradication.
Accordingly, in this survey, data will be collected from 500 patients to whom Takecab Tablets is administered for supplement of *H. pylori* eradication, and will be compared with the safety information of Takecab Tablets collected in the drug use surveillance in patients with acid-related diseases (total 3,000 patients) and with information provided in the package inserts of antimicrobials, and it will be confirmed whether there is a new safety concern or not (please note that the sample size of 500 patients is not statistically calculated).
In this survey, patients excluded from the clinical studies such as with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis will be enrolled.

4.0 Study population

Patients with the diseases described below* will receive triple therapy for *H. pylori* eradication. However, patients should meet the inclusion criterion and should not meet the exclusion criterion described below. Refer to the Precautions section of the package insert.

* If a patient's first-line eradication is unsuccessful in this survey, the patient can be enrolled in the second-line eradication in this survey.

Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, stomach following endoscopic treatment of early gastric cancer, or *H. pylori* gastritis

4.1 Inclusion criteria

Patients who meet either of the following criteria will be included in the survey:

[1] Patients receiving *H. pylori* eradication for the first time

[2] Patients for whom *H. pylori* eradication with Takecab Tablets or proton pump inhibitor + amoxicillin + clarithromycin was found unsuccessful and who are to receive eradication treatment with amoxicillin and metronidazole

4.2 Exclusion criteria

Patients who meet either of the following criteria will not be included in the survey. Refer to the Contraindications and Precautions section of the package insert of antimicrobials used in the triple therapy.

[1] Patients with previous history of hypersensitivity to ingredients in Takecab Tablets

[2] Patients receiving atazanavir sulfate or rilpivirine hydrochloride

5.0 Dosage and administration

The usual dose for adults is 20 mg of vonoprazan, 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. These three drugs will be orally administered at the same time, twice daily for 7 days. The dose of clarithromycin can be increased as clinically warranted. However, the dosage of clarithromycin should not exceed 400 mg (potency)/dose twice daily.

If *H. pylori* eradication with a three-drug regimen comprising vonoprazan or proton pump inhibitor + amoxicillin hydrate + clarithromycin is unsuccessful, as an alternative treatment, the following three drugs will be orally administered to adults at the same time, twice daily for 7 days: vonoprazan at a dose of 20 mg, amoxicillin hydrate at a dose of 750 mg (potency), and metronidazole at a dose of 250 mg. Refer to the Precautions section of the package insert of antimicrobials used in triple therapy.

6.0 Number of medical institutions by departments where the survey is planned

Internal medicine department (such as gastrointestinal medicine department)
Approximately 150 medical institutions

Hematology department Approximately 10 medical institutions

7.0 Method

7.1 Observational period

Triple therapy period (7 days) and the period from the completion of the triple therapy to the determination of *H. pylori* eradication

Time frame of the *H. pylori* determination is approximately from 4 weeks* to 2 months after the triple therapy.

* According to the "Guidelines for diagnosis and treatment of *H. pylori* infection" of the Japanese Society for *Helicobacter* Research, determination of *H. pylori* eradication should be conducted after 4 weeks

from discontinuation of eradication therapy.

7.2 Request to and contract with the medical institutions

Request to and contract with the medical institutions will be conducted using web-based electronic data collection system ([redacted]). The Medical Representative of [redacted] will explain objectives and details of this survey, procedure, electronic signature, and handling of user ID and password of [redacted] to the surveillance investigator based on “Request of the Drug use surveillance”, “Implementation guidance”, “Data entry screens of [redacted]” and “[redacted] operational manual [abbreviated version]” when this survey is requested. Thereafter, written contract is made with the medical institution and conduct of the survey will be requested within the prespecified duration of the survey.

7.3 Method of patient enrollment

Patients will be enrolled with “central enrollment method” using [redacted]. The surveillance investigator will enter the information required for patient enrollment (see Section 9.1) and will provide his/her electronic signature in [redacted] concerning patients to whom drugs of triple therapy (three drugs including Takecab Tablets) are prescribed within 5 days after prescription day of the three drugs including Takecab Tablets (the prescription day is defined as “Day 0”, and the day after prescription as “Day 1”) after term of contract with the medical institution is started.

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

The surveillance investigator will enter the information of patient demographics and treatment and will provide electronic signature in [redacted] for all patients enrolled in this survey by one month after completion of the observational period of each patient. If receipt of Takecab Tablets was not confirmed, it will be entered so in [redacted] (it is not required to enter other data).

For the patients who discontinued triple therapy including Takecab Tablets for any reason during the observational period, the surveillance investigator will enter the information of patient demographics and treatment and will provide his/her electronic signature in [redacted] by one month after completion of required observation. However, for patients who discontinued triple therapy including Takecab Tablets due to development of an AE, observation will be continued as much as possible until resolve or resolving from the AE even after the treatment is discontinued, and the observation results will be entered in [redacted] with his/her electronic signature.

7.5 Actions to take at the time of development of a serious adverse event

The surveillance investigator will immediately communicate [redacted] on development of a serious adverse event during the observational period. In addition, the surveillance investigator

will provide detailed information separately if requested by PPD .

8.0 Scheduled period of the survey

Duration of the survey: September 2015 to April 30, 2017

Patient enrollment period: September 2015 to February 28, 2017 Note)

Note) Patients will not be enrolled in this survey (or entered in CCI) on or after March 1, 2017 even if Takecab Tablets is prescribed on or before February 28, 2017.

If enrollment of the planned number of patients of this survey is completed prior to February 28, 2017, the patient enrollment will be discontinued prior to the end of the patient enrollment period. When the patient enrollment period is shortened, the duration of the survey is to be changed according to the shortened period.

9.0 Data to be collected

The surveillance investigator will enter the information of the following items in CCI .

The schedule of this survey is presented in the Appendix.

9.1 Patient enrollment

1) Data to be collected

Prescription date of the three drugs including Takecab Tablets used in the triple therapy; patient identification number; patient initials; sex; date of birth; target disease of *H. pylori* eradication; assessment of inclusion and exclusion criteria

2) Data collection period

At the time of patient enrollment

9.2 Patient demographic information

1) Data to be collected

Inpatient/outpatient classification (at the time when triple therapy is started); predisposition of hypersensitivity (presence/absence and details); complication (presence/absence and details); details of previous *H. pylori* eradication (in patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor with amoxicillin and clarithromycin); height; weight; smoking history; drinking history; diagnosis of *H. pylori* infection (time of diagnosis and testing method)

2) Data collection period

At the start of triple therapy

9.3 Information of treatment

1) Data to be collected

Treatment compliance to Takecab Tablets and antimicrobials used for triple therapy (name of drugs; daily dose; duration of triple therapy and reason for discontinuation of the triple

therapy); treatment compliance to concomitant drugs (excluding antimicrobials used for the triple therapy) (presence/absence; drug name(s), and indication(s))

2) Data collection period

Duration from the start to the completion (or the discontinuation) of triple therapy

9.4 Test/examination items

9.4.1 Determination of *H. pylori* eradication

1) Test items

Conduct of tests (presence/absence; reason if test is not conducted; testing method; date and result of determination)

2) Testing period

At the time of determination of *H. pylori* eradication*

* Time frame of the *H. pylori* determination is approximately from 4 weeks to 2 months after the triple therapy.

9.4.2 Liver function test

1) Test items

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

2) Testing period

Duration from the start of triple therapy* to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

* Within 1 month before starting triple therapy

9.4.3 Other examination items

1) Examination items

Presence/absence of pregnancy during the observational period (only female patients)
If pregnancy is confirmed during the observational period, the information is immediately communicated to PPD. The surveillance investigator provides detailed information (including information until delivery, e.g., pregnancy outcome such as premature delivery, as much as possible) according to the request from PPD.

2) Examination period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

9.5 Adverse event

1) Data to be collected

Presence/absence of adverse event (AE) (See Table 1); AE term; onset date; seriousness; and reason for seriousness (See Table 2); cause of discontinuation of triple therapy;

outcome date; outcome; causality* with triple therapy (See Table 3)

Follow-up survey will be conducted as much as possible when outcome is not resolved or unknown and causality is determined as unassessable.

Detailed information (e.g., clinical course and results of tests conducted for diagnosis) will be collected as much as possible when onset of hepatic function disorder or gastrointestinal infection of clostridium difficile is observed.

* Following information will be collected: rationale of assessment when causality is assessed as not related, and reason when causality is determined as unassessable.

Note) A point to consider concerning adverse events

Abnormal exacerbation of the target disease, i.e., exacerbation worse than the expected natural course of the disease will be handled as an adverse event, but expected exacerbation of the target disease will not be handled as an adverse event.

2) Data collection period

Duration from the start of triple therapy to the determination of *H. pylori* eradication (or the discontinuation of triple therapy)

Table 1 Definition of adverse event

Adverse event (AE) is any unfavorable medical occurrence in a patient administered a pharmaceutical product. It does not necessarily need to have a causal relationship with the pharmaceutical product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory values), symptom, or disease occurring at the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Following cases should also be handled as adverse events. • Symptoms developed in an infant breastfed by a mother receiving the pharmaceutical product • Symptoms developed in a child after administration of the pharmaceutical product • Symptoms developed after occupational exposure to the pharmaceutical product • Symptoms developed due to the use of a counterfeit of a pharmaceutical product manufactured/marketed by Takeda Pharmaceutical Company Limited

Table 2 Seriousness assessment criteria

An event meeting any of the following criteria is assessed as "serious":

1. Fatal (death)
2. Life-threatening (life-threatening)
3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization)
4. Results in persistent or significant disability/incapacity (disability)
5. Congenital anomaly/birth defect (congenital anomaly)
6. Other medically important condition than 1-5. Events listed in "Takeda Medically Significant AE List" are included in this criterion.

Takeda Medically Significant AE List

- Acute respiratory failure/Acute respiratory distress syndrome (ARDS)
- Anaphylactic shock
- Torsade de pointes/Ventricular fibrillation/Ventricular tachycardia
- Acute renal failure
- Malignant hypertension
- Pulmonary hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Pulmonary fibrosis (including interstitial pneumonia)
- Agranulocytosis
- Neuroleptic malignant syndrome/hyperthermia malignant
- Aplastic anaemia
- Abortion spontaneous/stillbirth and dead foetus
- Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Transmission or suspected transmission of infection via a medicinal product
- Hepatic necrosis
- Endotoxic shock or suspected endotoxic shock
- Acute hepatic failure

Table 3 Causality assessment criteria for adverse events and triple therapy

Assessment	Assessment criteria
Related	There is temporal relationship (including the clinical course after the discontinuation of the triple therapy). Or, while other factors such as underlying disease, complication, concomitant drug or concomitant procedure could be presumed, the AE is possibly related to triple therapy.
Not related	There is no temporal relationship with the triple therapy. Or, other factors such as underlying disease, complication, concomitant drug or concomitant procedure are quite considerable as the cause.
Unassessable	Information required for causality assessment, such as temporal relationship (including the clinical course after the discontinuation of the triple therapy), underlying disease, complication, concomitant drug, and concomitant procedure is insufficient.

10.0 Analysis items and method

10.1 Items related to patient disposition

Following data will be accumulated: number of patients enrolled; number of patients whose survey form (electronic) have been collected; number of patients in the safety analysis set and the efficacy analysis set; number of patients excluded from analysis and reasons for exclusion

10.2 Patient demographics

Patient demographic data including sex, age, hypersensitivity predisposition and complication will be accumulated.

10.3 Details of treatment

Treatment compliance to Takecab Tablets and antimicrobials used for the triple therapy and concomitant drugs (other than antimicrobials used for the triple therapy) will be accumulated.

10.4 Items related to safety

Following data will be accumulated for the safety analysis set. Adverse events are coded with MedDRA/J, and accumulated by Preferred Term (PT) and System Organ Class (SOC).
The patients enrolled to this survey in both first-line and second-line eradication cases will be accumulated separately.

10.4.1 Onset of adverse events

Frequencies of adverse events which developed during the observational period will be accumulated by type, onset period, seriousness, and causality with the triple therapy.

10.4.2 Factors which may affect safety

Frequencies of adverse reactions which developed during the observational period will be accumulated by subgroups of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; presence/absence of renal disorder complication; and presence/absence of liver disorder complication) and details of treatment (first-line and second-line eradication).

10.5 Items related to efficacy

Following data will be accumulated for the efficacy analysis set.

10.5.1 Eradication rate of *H. pylori*

In patients who have the result of determination of eradication, proportion of patients with *H. pylori* negative (eradication rate) will be accumulated by first-line and second-line eradication.

10.5.2 Factors which may affect efficacy

The eradication rates of *H. pylori* will be accumulated by subgroup of patient demographic factors (e.g., sex; age; target disease of *H. pylori* eradication; complication).

11.0 Registration of survey information

Takeda Pharmaceutical Company Limited will register information of this survey on the public websites before starting this survey.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- Registration system of clinical trials of National Institutes of Health: ClinicalTrials.gov

12.0 Organization of this survey

12.1 Manager

Takeda Pharmaceutical Company Limited

Post-marketing surveillance manager

13.0 Clinical research organizations

PPD

14.0 Other required items

14.1 Revision of the protocol

During the period of conducting this survey, following information will be captured: development of ADRs not expectable from Precautions for Use and onset of serious ADRs; whether there is increased frequency of specific ADRs or not; validity of the survey items. The protocol will be reviewed and revised if it is considered necessary. In addition, if a supplemental approval of a new dosage and administration or a new indication is granted during the period of conducting this survey, necessity of revision of the protocol will be examined if needed, and the protocol will be revised if needed.

14.2 Procedure when there is any issue or doubt

If there is any safety or efficacy issue, data will be closely examined, and action will be considered.

Appendix: Observation schedule

Data to be collected \ Period of survey/data entry		Observational period				
		At the time of patient enrollment	At the start of triple therapy	At the completion of triple therapy	At the time of determination of *H. pylori* eradication Note 1)	At the time of discontinuation of triple therapy
Patient enrollment	Prescription date of 3 drugs including Takecab Tablets in triple therapy	○				
	Patient identification number	○				
	Patient initials	○				
	Sex	○				
	Date of birth	○				
	Target disease of *H. pylori* eradication	○				
	Assessment of inclusion criteria	○				
	Assessment of exclusion criteria	○				
Patient demographic information	Inpatient/outpatient classification		○			
	Hypersensitivity predisposition		○			
	Complication		○			
	Previous *H. pylori* eradication Note 2)		○			
	Height, weight		○			
	Smoking history		○			
	Drinking history		○			
	Diagnosis of *H. pylori* infection		○			
Information of treatment	Treatment compliance to Takecab Tablets and antimicrobials		←○→			○
	Treatment compliance to concomitant drugs (excluding antimicrobials)		←○→			○
Test/ examination items	Determination of *H. pylori* eradication				○	
	Liver function test		←○Note 3)→			○
	Presence/absence of pregnancy (only female patients)		←○→			○
	Adverse event		←○→			○

○ : To be conducted

←○→ : To be conducted throughout the period

Note 1) Approximately from 4 weeks to 2 months after the triple therapy is completed

Note 2) In patients with a history of unsuccessful *H. pylori* eradication with Takecab Tablets or a proton pump inhibitor in combination with amoxicillin and clarithromycin

Note 3) From within one month before the start of triple therapy to determination of *H. pylori* eradication