

Review Report

January 10, 2014

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Takelda Combination Tablets
[Non-proprietary name]	Aspirin/Lansoprazole (JAN*)
[Name of applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 27, 2013
[Dosage form/Strength]	Each tablet contains 100 mg of aspirin and 15 mg of lansoprazole.
[Application classification]	Prescription drug (2) New prescription combination drug
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

* *Japanese Accepted Name (modified INN)*

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Review Results

January 10, 2014

[Brand name] Takelda Combination Tablets
[Non-proprietary name] Aspirin/Lansoprazole
[Name of applicant] Takeda Pharmaceutical Company Limited
[Date of application] March 27, 2013
[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that Takelda Combination Tablets can be expected to have the same efficacy and safety profile as the coadministration of low-dose aspirin with lansoprazole in patients with a history of gastric or duodenal ulcers requiring long-term treatment with low-dose aspirin.

As a result of its regulatory review, PMDA has concluded that Takelda Combination Tablets may be approved for the indication and dosage and administration as shown below.

[Indication] Reduction of the risk of thrombosis and embolism in patients who have a history of gastric ulcer or duodenal ulcer and who:

- Have angina pectoris (chronic stable angina and unstable angina), myocardial infarction, and ischemic cerebrovascular diseases (transient ischemic attack [TIA] and cerebral infarction) or
- Underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)

[Dosage and administration] The usual adult dosage is one tablet (containing 100 mg of aspirin and 15 mg of lansoprazole) administered orally once daily.

Review Report (1)

November 21, 2013

I. Product Submitted for Registration

[Brand name]	Takelda Combination Tablets
[Non-proprietary name]	Lansoprazole/Aspirin
[Name of applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 27, 2013
[Dosage form/Strength]	Each tablet containing 15 mg of lansoprazole and 100 mg of aspirin
[Proposed indication]	Reduction of the risk of thrombosis and embolism and prevention of recurrent gastric or duodenal ulcers associated with low-dose aspirin in patients who: <ul style="list-style-type: none">• Have angina pectoris (chronic stable angina and unstable angina), myocardial infarction, and ischemic cerebrovascular diseases (transient ischemic attack [TIA] and cerebral infarction) or• Underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)
[Proposed dosage and administration]	The usual adult dosage is one tablet (containing 15 mg of lansoprazole and 100 mg of aspirin) administered orally once daily.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

The proposed product “Takelda Combination Tablets” (the LPZ/ASP combination product) is a combination product of lansoprazole and aspirin. In the context of the combined use of lansoprazole and aspirin, lansoprazole is already approved for the indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin.” Accordingly, no non-clinical data were submitted in the application for this new combination drug.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The LPZ/ASP combination product is a combination formulation containing the active ingredients lansoprazole, a proton pump inhibitor, and aspirin, a cyclooxygenase-1 inhibitor.

In Japan, Takepron Capsules 15 and Takepron Capsules 30, the capsule forms of lansoprazole, were approved for the indications of “gastric ulcers, duodenal ulcers, anastomotic ulcers, reflux esophagitis,

and Zollinger-Ellison syndrome” in October 1992 and for the additional indication of “adjuvant therapy for *Helicobacter pylori* eradication in patients with gastric or duodenal ulcers” in September 2000. The orally disintegrating (OD) forms of lansoprazole, Takepron OD Tablets 15 and Takepron OD Tablets 30, were approved in March 2002 for the same indications as those for Takepron Capsules 15 and Takepron Capsules 30 at that time. Subsequently, Takepron Capsules 15 and Takepron OD Tablets 15 were approved for the additional indications of “non-erosive reflux disease” in June 2006, “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” in July 2010, and “prevention of recurrent gastric or duodenal ulcers associated with nonsteroidal anti-inflammatory drugs (NSAID)” in August 2010. Takepron Capsules 15, Takepron Capsules 30, Takepron OD Tablets 15, and Takepron OD Tablets 30 were approved for the additional indications of “adjuvant therapy for *Helicobacter pylori* eradication in the stomach following the endoscopic treatment of gastric mucosa associated lymphoid tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, or early gastric cancer” in June 2010 and “adjuvant therapy for *Helicobacter pylori* eradication in patients with gastritis induced by *Helicobacter pylori* infection” in February 2013. In addition, Takepron Intravenous 30 mg, an injection form of lansoprazole, was approved for the indication of “treatment of the diseases that preclude oral administration: gastric ulcers, duodenal ulcers, acute stress ulcers, and acute gastric mucosal lesions, which are associated with bleeding” in October 2006. Low-dose aspirin tablet products (e.g., Bayaspirin 100 mg, Bufferin Combination Tablet A81) were approved for the indications of “reduction of the risk of thrombosis and embolism in patients with angina pectoris (chronic stable angina and unstable angina), myocardial infarction, and ischaemic cerebrovascular disorder (transient ischaemic attack [TIA], cerebral infarction)” and “reduction of the risk of thrombosis and embolism following coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA)” in September 2000 and for the additional indication of “Kawasaki’s disease (and cardiovascular sequelae of Kawasaki’s disease)” in October 2005.

Aspirin derives its antiplatelet activity by blocking cyclooxygenase-1 while causing gastric and duodenal ulcers as adverse reactions. Lansoprazole derives its antiulcer activity by suppressing acid secretions through inhibition of the proton pump which is the final step of the mechanism of acid secretion in gastric parietal cells.

Given that lansoprazole is indicated for “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” the applicant considered that combining lansoprazole with low-dose aspirin would help reduce the adverse reactions associated with the latter and thus embarked on development of the LPZ/ASP combination product.

Takeda Pharmaceutical Company Limited began developing the LPZ/ASP combination product in 20█. Takeda has recently submitted a marketing application for the LPZ/ASP combination product for use in patients with a history of gastric or duodenal ulcer who require long-term aspirin treatment, presenting the results of Japanese clinical studies and other data. The LPZ/ASP combination product is not under

review for marketing approval, approved, or marketed in any country outside Japan.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substances

2.A.(1.1) Lansoprazole

Lansoprazole is identical to the drug substance used in “Takepron Intravenous 30 mg,” an approved product manufactured and marketed by the applicant.

2.A.(1.2) Aspirin

[REDACTED]

2.A.(2) Drug product

2.A.(2.1) Description and composition of the drug product and formulation development

The drug product is a tablet consisting of an outer layer containing enteric-coated granules consisting of 15 mg of lansoprazole and an enteric-coated inner core containing 100 mg of aspirin. As excipients, the drug product contains cornstarch, microcrystalline cellulose, carmellose, methacrylic acid copolymer LD, ethyl acrylate and methyl methacrylate copolymer dispersion, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, lactose/microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, macrogol 6000, yellow iron sesquioxide, iron sesquioxide, D-mannitol, crospovidone, magnesium aluminometasilicate, and magnesium stearate.

2.A.(2.2) Manufacturing process

[REDACTED]

Critical process parameters (CPPs) were identified based on the quality attributes determined by the risk assessment performed using failure mode effects analysis. Preliminary experiments for the identified CPPs were conducted to establish the manufacturing conditions.

2.A.(2).3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (ultraviolet-visible spectrophotometry [UV]), purity (related substances [high performance liquid chromatography (HPLC)]), uniformity of dosage units (uniformity of content test [HPLC]), dissolution (acid-resistance test) (paddle method [UV for lansoprazole and HPLC for aspirin]), dissolution (buffer solution test) (paddle method [HPLC]), and assay (HPLC).

2.A.(2).4 Stability of drug product

Table 1 shows the results of major stability tests of the drug product. Photostability testing showed that the drug product was stable when exposed to light.

Table 1. Stability tests of drug product

Test	Primary batches	Temperature	Humidity	Storage forms	Storage period
Long-term testing	3 pilot scale batches	25°C	60% RH	[REDACTED]	18 months
Accelerated testing		40°C	75% RH	[REDACTED]	6 months

a: Press Through Package ([REDACTED])

[REDACTED]
[REDACTED]
[REDACTED] The long term study is scheduled to continue for 36 months.

2.B Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substances and drug product are appropriately controlled.

3. Clinical data

3.(i) Summary of biopharmaceutic studies and associated analytical methods

3.(i).A Summary of the submitted data

Concentrations of lansoprazole and aspirin in human plasma were determined with a validated liquid chromatography-tandem mass spectroscopy (LC-MS/MS) procedure. The lower limits of quantification for plasma concentrations of lansoprazole and aspirin were 5 ng/mL and 2 ng/mL, respectively.

Unless otherwise stated, pharmacokinetic parameters are expressed as mean \pm standard deviation.

3.(i).A.(1) Japanese phase I clinical study (protocol no. CPH-001, 5.3.1.2-1 [REDACTED] 20[REDACTED] to [REDACTED] 20[REDACTED])

Studies 1 and 2 of Study CPH-001 were conducted in healthy Japanese adult men confirmed to have the cytochrome P450 (CYP) 2C19 extensive metabolizer genotype. Study 1 was conducted to evaluate the

bioequivalence (BE) of lansoprazole and aspirin between a single dose of a combination tablet containing 15 mg of lansoprazole and 100 mg of aspirin (L15/A100 mg tablet) and coadministration of a single dose of a lansoprazole 15 mg OD tablet (Takepron OD Tablet) and an aspirin 100 mg enteric-coated tablet (Bayaspirin). Study 2 was conducted to evaluate the effects of food on the pharmacokinetics of lansoprazole and aspirin following a single dose of the L15/A100 mg tablet.

The combination products A and B, of which the latter is the proposed commercial formulation, were used as the L15/A100 mg tablets. [REDACTED]

Study 1 consisted of a preliminary study and a main study. The combination product A and the proposed commercial combination product B were used in the preliminary study of Study 1, which evaluated BE of lansoprazole and aspirin between the administration of the combination products and coadministration of single-agent drugs. The combination product B was used in the main study of Study 1, which evaluated BE of lansoprazole between the administration of the combination product and coadministration of single-agent drugs.

3.(i).A.(1.1) Study 1 (BE evaluation)

3.(i).A.(1.1).(a) Preliminary study (evaluation of BE for lansoprazole and aspirin)

A two-treatment, two-period, crossover study was conducted in 48 healthy Japanese adults to evaluate BE of lansoprazole and aspirin between the administration of the combination product A and the coadministration of a lansoprazole 15 mg OD tablet and an aspirin 100 mg enteric-coated tablet and between the administration of the combination product B and the coadministration of a lansoprazole 15 mg OD tablet and an aspirin 100 mg enteric-coated tablet (4 groups [12 subjects/group], washout period ≥ 14 days). The study drug was administered as a single oral dose without breakfast.

The geometric mean ratios (two-sided 90% confidence interval [CI]) of the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 24 hours after administration (AUC_{0-24}) for lansoprazole following administration of the combination product A to those following coadministration of single-agent drugs were 1.214 [1.012-1.455] and 1.180 [1.073-1.298], respectively. The geometric mean ratios of C_{max} and AUC_{0-12} for aspirin following administration of the combination product A to those following coadministration of single-agent drugs were 1.266 [0.896-1.789] and 1.223 [0.901-1.661], respectively, (n = 23).

The geometric mean ratios of C_{max} and AUC_{0-24} for lansoprazole following administration of the combination product B to those following coadministration of single-agent drugs were 1.134 [0.958-1.343] and 1.064 [0.976-1.159], respectively. The geometric mean ratios of C_{max} and AUC_{0-12} for aspirin following administration of the combination product B to those following coadministration of single-

agent drugs were 1.015 [0.765-1.347] and 0.974 [0.827-1.146], respectively, (n = 24). The geometric mean ratios [two-sided 90% CI] of C_{\max} for lansoprazole and aspirin did not satisfy the BE criteria of the “Guidelines for Bioequivalence Studies of Generic Products” (PMSB/ELD Notification No. 487 dated December 22, 1997; the Guideline was partially amended by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) (hereafter referred to as “Generic BE Guidelines”).

3.(i).A.(1).1.(b) Main study (evaluating BE of lansoprazole)

The findings of the preliminary study substantiated BE of aspirin based on a dissolution test conducted according to the Generic BE Guidelines, but necessitated a study in humans for lansoprazole [see “3.(i).A.(2) Evaluation of dissolution profile of aspirin”]. Accordingly, a two-treatment, two-period, crossover study was conducted in 230 healthy Japanese adults to evaluate BE of lansoprazole alone between the administration of the combination product B and coadministration of a lansoprazole 15 mg OD tablet and aspirin 100 mg enteric-coated tablet (washout period \geq 14 days). The study drug was administered as a single oral dose without breakfast.

The geometric mean ratios [two-sided 90% CI] of C_{\max} and AUC_{0-24} for lansoprazole following administration of the combination product B to those following coadministration of the single-agent drugs were 1.121 [1.068-1.177] and 1.075 [1.046-1.104], respectively, (n = 227), which satisfied the acceptance criteria for BE in the Generic BE Guidelines.

3.(i).A.(1).2) Study 2 (evaluation of food effects)

A two-treatment, two-period, crossover study was conducted in 24 healthy Japanese adults to evaluate the effects of food on the pharmacokinetics of lansoprazole and aspirin in association with the administration of the combination products A and B (4 groups [6 subjects/group], washout period \geq 14 days). The study drug was administered as a single oral dose without breakfast or 30 minutes after the start of breakfast. The following results are for the combination product B, which is the proposed commercial formulation.

Following a single oral dose of the combination product B under fasting conditions and after a meal, the median time to C_{\max} (t_{\max}) for lansoprazole was 1.0 and 4.0 hours, respectively, the C_{\max} was 503.9 ± 191.18 and 370.1 ± 171.03 ng/mL, respectively, the $AUC_{0-\text{inf}}$ was 1132 ± 551.29 and 1004 ± 488.40 ng·h/mL, respectively, and the elimination half-life ($t_{1/2}$) was 1.201 ± 0.39062 and 1.184 ± 0.40887 hours, respectively. The geometric mean ratios [two-sided 90% CI] of C_{\max} and $AUC_{0-\text{inf}}$ of lansoprazole taken after a meal to those following administration under fasting conditions were 0.721 [0.531-0.980] and 0.893 [0.767-1.039], respectively, (n = 11).

Following a single oral dose of the combination product B under fasting conditions and after a meal, the median t_{\max} for aspirin was 3.5 and 5.5 hours, respectively, the C_{\max} was 666.6 ± 313.82 and 634.6 ± 193.40 ng/mL, respectively, the $AUC_{0-\text{inf}}$ was 833.5 ± 250.42 and 769.2 ± 168.19 ng·h/mL, respectively,

and the $t_{1/2}$ was 0.4776 ± 0.20372 and 0.5361 ± 0.17007 hours, respectively. The geometric mean ratios of C_{max} and AUC_{0-inf} of aspirin taken after a meal to that taken under fasting conditions were 0.980 [0.693-1.386] and 0.929 [0.722-1.194], respectively, (n = 11).

3.(i).A.(2) Evaluation of dissolution profile of aspirin (5.3.1.2-4)

The point estimates of the geometric mean ratios in the preliminary study of Study 1, which evaluated BE in 24 subjects, fell within the range of 0.90 to 1.11. Thus, the similarity of the dissolution profiles of aspirin was evaluated in a dissolution test conducted according to the Generic BE Guidelines, in order to investigate the BE of aspirin between the administration of the combination product B and the coadministration of an aspirin 100 mg enteric-coated tablet and lansoprazole 15 mg OD tablet under the Generic BE Guidelines.

As a result of the test in 12 vessels under each set of conditions, the dissolution profile of the combination product B was considered to be similar to that of the aspirin 100 mg enteric-coated tablet at the time of the test. However, after the main study of Study CPH-001 in which BE was evaluated for lansoprazole, flaws were identified in the analyses for assessing the results of the dissolution test, and it was determined that the acceptance criteria for dissolution profile similarity specified in the Generic BE Guidelines were not satisfied under the condition of pH [REDACTED] and [REDACTED]. Given the results of the preliminary investigation, which was based on these findings, the dissolution test was conducted with [REDACTED] vessels under each set of conditions.

The results of the dissolution test did not satisfy the acceptance criteria for dissolution profile similarity specified in the Generic BE Guidelines under the condition of pH [REDACTED] and [REDACTED], failing to substantiate BE for aspirin.

3.(i).B Outline of the review by PMDA

The applicant provided the following explanation about the BE of aspirin and lansoprazole between the administration of the LPZ/ASP combination product and coadministration of the single-agents:

The two-sided 90% confidence intervals of the geometric means ratios of AUC for lansoprazole and aspirin in the CPH-001 preliminary study fell within the range of the BE acceptance criteria specified in the Generic BE Guidelines [0.80-1.25], but the study did not show BE between the LPZ/ASP combination product and concomitant use of the single-agent drugs as the C_{max} values did not fall within the range of the acceptance criteria.

The main study of Study CPH-001 was conducted in 230 healthy Japanese men because the point estimate of the geometric mean ratio of C_{max} for lansoprazole did not fall within the range of 0.90 to 1.11. In the study, the two-sided 90% confidence interval of the geometric mean ratio of C_{max} for lansoprazole fell within the range of 0.80 to 1.25, substantiating the BE between the LPZ/ASP combination product and the coadministered single-agent drugs.

A dissolution test (12 vessels under each set of conditions) was conducted according to the Generic BE Guidelines because the point estimate of the geometric mean ratio of C_{max} for aspirin fell within the range of 0.90 to 1.11. The similarity of the dissolution profiles was considered to substantiate the BE of aspirin between the LPZ/ASP combination product and the coadministered single-agent drugs. The dissolution test results, however, were reviewed after conducting the main study of Study CPH-001, and calculation of the f2 function according to the Generic BE Guidelines revealed that the acceptance criteria for dissolution profile similarity were not satisfied under the condition of pH [REDACTED] and [REDACTED]. The results of the preliminary investigation, which was based on these findings, further revealed large variability among the measurements of the reference formulation under the condition of pH [REDACTED] and [REDACTED]. After an investigation of the cause of variability in the aspirin dissolution profile of the reference formulation, the variability was found to be attributed to coincidental factors. Thus, in order to assess the dissolution profile similarity, it was considered appropriate to conduct a new dissolution test with [REDACTED] vessels ([REDACTED] vessels for the condition of pH [REDACTED] and [REDACTED])¹ taking account of the variability in the aspirin dissolution profiles. A newly conducted dissolution test, however, did not demonstrate dissolution profile similarity because the test results did not meet the acceptance criteria under the condition of pH [REDACTED] and [REDACTED], although the results met the acceptance criteria under the conditions of pH [REDACTED] and [REDACTED], pH [REDACTED] and [REDACTED], and pH [REDACTED] and [REDACTED]. The BE of aspirin between the LPZ/ASP combination product and the coadministered single-agent drugs was thus not substantiated. Showing the BE of aspirin between the LPZ/ASP combination product and the coadministered single-agent drugs in a human BE study would require an enrollment of 160 healthy adults.

PMDA considers as follows:

In general, when a combination product is developed using approved drug products, the BE of a combination product to the coadministered individual single-agent drugs should be demonstrated. The BE of lansoprazole in the LPZ/ASP combination product and the coadministered single-agent drugs was shown in the main study of Study CPH-001, as the two-sided 90% confidence intervals of the geometric mean ratios of AUC_{0-24} and C_{max} fell within the ranges of the acceptance criteria for BE specified in the Generic BE Guidelines. However, the results of the preliminary study of Study CPH-001 and the dissolution test conducted to substantiate the BE of aspirin between the LPZ/ASP combination product and the coadministered single-agent drugs did not show dissolution profile similarity. The study results available to the present, do not substantiate the BE of aspirin between the LPZ/ASP combination product and the coadministered single-agent drugs. The pharmacokinetics of aspirin should have been evaluated in the main study of Study CPH-001, but no such evaluation was planned because the main study of Study CPH-001 had already been conducted when flaws were identified in the analyses for assessing the results of the dissolution test. Based on this situation, an additional human study for evaluating BE

¹ The dissolution test was performed with [REDACTED] vessels for the pH [REDACTED] condition alone because the results of the preliminary investigation showed that aspirin does not dissolve from the combination product B and the aspirin 100 mg enteric-coated tablet under the pH [REDACTED] and [REDACTED] conditions.

of aspirin should be conducted if the applicant intends to proceed with their development policy of the LPZ/ASP combination product, that is, to show the BE of lansoprazole and aspirin between the LPZ/ASP combination product and the coadministered single-agent drugs. Nevertheless, it is a common acknowledgement among the areas of medical and pharmaceutical science that the therapeutic benefit of low-dose aspirin must be shown at doses of 75 to 325 mg/day to reduce the risk of thrombosis and embolism in patients with angina pectoris (chronic stable angina and unstable angina) etc., or during postoperative period, and many products with different pharmacokinetic profiles such as antacid buffered and enteric-coated products have been approved. In view of this situation and the pharmacokinetic profiles of the active ingredients of the LPZ/ASP combination product determined in the investigations conducted to substantiate BE, whether it is possible to determine that the LPZ/ASP combination product may be provided to clinical settings will be discussed in the clinical section [see “3.(iii).B.(2) Aspirin”].

3.(ii) Summary of clinical pharmacology studies

3.(ii).A Summary of the submitted data

3.(ii).A.(1) Drug interaction study (protocol no. GB [REDACTED]/131, 5.3.3.1-1 [REDACTED] 19[REDACTED] to [REDACTED] 19[REDACTED]), Reference data)

A multiple-dose pharmacokinetic drug interaction study was conducted for lansoprazole and non-steroidal antiinflammatory drugs (NSAIDs; aspirin, indomethacin, and ibuprofen) in 24 healthy non-Japanese men (8 per group). The NSAIDs were administered from Days 1 to 15 followed by an 8-day washout period and then again administered from Days 24 to 28. Lansoprazole was administered from Days 8 to 15. Sixty mg of lansoprazole was administered once daily and 300 mg of aspirin was administered 3 times daily, and the effects of lansoprazole on the pharmacokinetics of aspirin were evaluated by assessing the pharmacokinetics of aspirin at the following time points: before lansoprazole coadministration (Day 5), during coadministration (Day 15), and after coadministration (Day 28). The geometric mean ratios [two-sided 90% CI] of the C_{max} and AUC_{0-inf} for aspirin of those during lansoprazole coadministration (Day 15) to those before coadministration (Day 5) were 1.088 [0.864-1.312] and 0.916 [0.691-1.142], respectively, and of those after lansoprazole coadministration (Day 28) to those before coadministration (Day 5) were 1.136 [0.912-1.360] and 1.070 [0.845-1.296], respectively.

3.(ii).B Outline of the review by PMDA

The applicant explained the pharmacokinetic drug interactions between aspirin and lansoprazole as follows:

After undergoing hydrolysis, aspirin is metabolized to conjugates and excreted primarily in the urine. Lansoprazole and its metabolites are primarily excreted via the bile in the feces. Pharmacokinetic drug interactions between lansoprazole and aspirin are unlikely because the 2 drugs are metabolized mainly by different enzymes and excreted through different routes.

PMDA considers as follows:

The results of Study GB [REDACTED]/131 indicate that lansoprazole does not substantially affect the pharmacokinetics of aspirin. Although the effects of aspirin on the pharmacokinetics of lansoprazole were not evaluated in Study GB [REDACTED]/131, clinically significant pharmacokinetic drug interactions between aspirin and lansoprazole are unlikely, because the metabolism and excretion characteristics of aspirin and lansoprazole indicate no major concerns about pharmacokinetic drug interactions between the 2 ingredients, and patients on low-dose aspirin to reduce the postoperative risk of thrombosis and embolism or in association with a disease such as angina pectoris (chronic stable angina, unstable angina) have not been shown to experience an increase in thromboembolism when taking lansoprazole concomitantly.

3.(iii) Summary of clinical efficacy and safety

3.(iii).A Summary of the submitted data

The results of one Japanese phase I study were submitted as the evaluation data. [see “3.(i) Summary of biopharmaceutic studies and associated analytical methods” and “3.(ii) Summary of clinical pharmacology studies” for more information on BE and pharmacokinetics].

3.(iii).A.(1) Japanese phase I clinical study (protocol no. CPH-001, 5.3.1.2-1 [REDACTED] 20 [REDACTED] to [REDACTED] 20 [REDACTED]))

Studies 1 and 2 of Study CPH-001 were conducted in healthy Japanese adult men confirmed to have the CYP2C19 extensive metabolizer genotype at 2 medical institutions in Japan. Study 1 was a two-treatment, two-period crossover study conducted to evaluate BE following a single dose of L15/A100 mg tablets and the coadministration of a single dose of lansoprazole 15 mg OD tablet and aspirin 100 mg enteric-coated tablet. Study 2 was conducted to evaluate the effects of food on the pharmacokinetics of lansoprazole and aspirin following a single dose of the L15/A100 mg tablet (washout period \geq 14 days).

Study 1 consisted of a preliminary study and main study. The BE between the combination products A or B and the coadministration of single-agent drugs was evaluated in the preliminary study of Study 1, which had a target sample size of 12 subjects per group for a total of 48 subjects. The BE between the combination product B and the coadministration of single-agent drugs was evaluated in the main study of Study 1, which had a target sample size of 115 subjects per group for a total of 230 subjects. The effects of food on the combination products A and B were evaluated in Study 2, which had a target sample size of 6 subjects per group for a total of 24 subjects.

In the preliminary and main studies of Study 1, the subjects orally received a single dose of L15/A100 mg tablet or lansoprazole 15 mg OD tablet with aspirin 100 mg enteric-coated tablet without breakfast. In Study 2, the subjects orally received a single dose of L15/A100 mg tablet without breakfast or 30 minutes after the start of breakfast.

The safety results of the studies are shown below.

3.(iii).A.(1.1) Preliminary study of Study 1

Twenty-four subjects for the evaluation of the combination product A and 24 subjects for the evaluation of the combination product B were enrolled in the preliminary study of Study 1. All subjects were included in the safety analysis population.

In the evaluation of combination product A, an adverse event (1 event of presyncope) was reported in 1 subject following a single dose of the coadministration of lansoprazole 15 mg OD tablet and aspirin 100 mg enteric-coated tablet. No adverse events were reported in the evaluation of the combination product B. No deaths or serious adverse events were reported in either evaluation.

3.(iii).A.(1.2) Main study of Study 1

Two hundred thirty subjects were enrolled in the main study of Study 1. All subjects were included in the safety analysis population.

Adverse events were reported in 5 subjects following the administration of the combination product B (4 events of alanine aminotransferase [ALT] increased, 1 event of aspartate aminotransferase [AST] increased, and 1 event of arthropod sting) and in 2 subjects following a single-dose coadministration of lansoprazole 15 mg OD tablet and aspirin 100 mg enteric-coated tablet (1 event of ALT increased and 1 event of eosinophil count increased). No deaths or serious adverse events were reported.

3.(iii).A.(1.3) Study 2

Twelve subjects for the evaluation of the combination product A and 12 subjects for the evaluation of the combination product B were enrolled in Study 2. All subjects were included in the safety analysis population.

In the evaluation of the combination product A, an adverse event was reported in 1 subject following postprandial administration (1 event of eosinophil count increased). In the evaluation of the combination product B, an adverse event was reported in 1 subject receiving the drug under fasting conditions (1 event of blood bilirubin increased) and in 1 subject following postprandial administration (1 event of ALT increased and 1 event of AST increased). No deaths or serious adverse events were reported in either evaluation.

3.(iii).B *Outline of the review by PMDA*

3.(iii).B.(1) The significance of combining the ingredients

The applicant provided the following explanation of the significance of developing the co-formulation of the two active ingredients:

A low-dose aspirin product was approved as an antiplatelet drug in September 2000 at the following dosage and administration; “The usual adult dosage is 100 mg of aspirin given orally once daily. The

dose may be increased to 300 mg according to symptoms.” The Guidelines for Management of Anticoagulant and Antiplatelet Therapy in Cardiovascular Disease (Japanese Circulation Society 2009, presented by the 2008 Japanese Circulation Society Joint Working Group) recommends doses of 81 to 162 mg/day of aspirin for patients with a history of ischaemic heart diseases (e.g., long-term use of aspirin for unstable angina, stable effort angina, myocardial infarction [non-acute stage], CABG). The Japanese Guidelines for the Management of Stroke 2009 (Joint Committee on Guidelines for the Management of Stroke) recommends antiplatelet therapy for preventing recurrence of non-cardiogenic cerebral infarction, presenting 75 to 150 mg/day of aspirin as, currently, one of the most effective antiplatelet therapies in the prevention of recurrence of non-cardiogenic cerebral infarction.

Aspirin doubles the risk of gastrointestinal tract complications (bleeding, perforation) in middle-aged patients without a history of peptic ulcers or receiving no other drugs, and dramatically increases the risk of gastrointestinal bleeding in patients who have a history of peptic ulcers, who have a *Helicobacter pylori* infection, who are at least 60 years of age, or who are receiving drugs such as an NSAID, corticosteroid, clopidogrel, or anticoagulants (Hiraishi H and Shimada T. *Medicina*. 2012;49:66-69). Through their Expert Consensus Document (Bhatt DL et al. *Circulation*. 2008;118:1894-909), the American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and American Heart Association (AHA) advocate the use of a proton pump inhibitor (PPI), to prevent upper gastrointestinal bleeding associated with antiplatelet therapy in patients with a history of ulcer complications, history of non-bleeding peptic ulcers, or who have gastrointestinal bleeding, dual antiplatelet therapy, or anticoagulant therapy. In a therapeutic statement in the “Evidence-based Guideline for Gastric Ulcers, 2nd Edition” (Study Group on application and Evaluation of Guidelines for Gastric Ulcers. Jiho Inc. 2007), PPIs use is presented for the prevention of ulcer recurrence in patients on low-dose aspirin. We therefore thought it suitable to start the concomitant use of PPI soon in patients with a history of ischaemic heart diseases, ischaemic cerebrovascular disorder, or similar conditions who require long-term treatment with aspirin to prevent recurrent upper gastrointestinal bleeding if they have a history of gastric or duodenal ulcers.

In a clinical study of Takepron Capsules 15 and Takepron OD Tablets 15 conducted at the time of approval for the indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin,” lansoprazole 15 mg was orally administered once daily for 12 to 30 months to compare the preventive effect on gastric or duodenal ulcer and safety with those of gefarnate (an active comparator). Subjects of this study were patients who required long-term low-dose aspirin for the prevention of thrombosis or embolism due to angina pectoris, myocardial infarction, ischaemic cerebrovascular disorder, CABG or PTCA and who also had a history of gastric or duodenal ulcers. The study results showed that lansoprazole reduced the recurrence of gastric and duodenal ulcers as adverse reactions of low-dose aspirin as compared with gefarnate. Thus, “Reduction of adverse reactions (toxicity)” in “Points to Consider for Data Submitted in Application for Approval of New Drugs” (PFSB/ELD Notification No. 0331009, dated March 31, 2005) is valid as a reason for approval of the

LPZ/ASP combination product as a combination drug. Combining the 2 ingredients (lansoprazole and low-dose aspirin) into a single combination drug would improve convenience and compliance, which would in turn maximize the efficacy of lansoprazole and low-dose aspirin used together.

In conclusion, providing lansoprazole and low-dose aspirin as a combination drug is highly significant in clinical use.

PMDA considers as follows:

Japanese and non-Japanese guidelines recommend the coadministration of a PPI for the prevention of recurrence of aspirin-induced gastric or duodenal ulcers in patients who require treatment with low-dose aspirin and have a history of gastric or duodenal ulcers. Lansoprazole has been shown in Japanese clinical studies to reduce the recurrence rate of clinically significant gastric or duodenal ulcers as adverse reactions of low-dose aspirin and is approved for the indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin.” Accordingly, it is concluded that providing lansoprazole and low-dose aspirin in a combination drug is significant.

3.(iii).B.(2) Aspirin

The applicant provided the following explanation on why the BE of aspirin between the LPZ/ASP combination product and the approved products was not shown:

Only 2 low-dose aspirin products are approved as antiplatelet drugs in Japan. These products are an enteric-coated aspirin tablet (with 100 mg of aspirin) and an antacid buffered aspirin tablet (with 81 mg of aspirin). Although neither of them underwent clinical studies for marketing approval to evaluate efficacy and safety in Japan, the products were approved for the indications of “reduction of the risk of thrombosis and embolism in patients with angina pectoris (chronic stable angina, unstable angina), myocardial infarction, and ischaemic cerebrovascular disorder (TIA, cerebral infarction)” and “reduction of the risk of thrombosis and embolism following CABG and PTCA” based on the common acknowledgement among the societies of medical and pharmaceutical science in the efficacy and safety of low-dose aspirin. No close evaluations of the dosage were conducted in Japanese subjects in clinical studies. At the time of approving the two products, it was considered that “the dosage range of a low-dose aspirin, in which the effect of inhibiting platelet aggregation can be observed, is 75 to 325 mg/day”, and the approved dosage ranges for the enteric-coated aspirin tablets and the buffered aspirin tablets were broad, i.e., 100 to 300 mg once daily and 81 to 324 mg once daily, respectively. Although the mean C_{max} values of the two products differ, both are used in clinical practice as therapeutically beneficial drugs for the same indication.

Although the two-sided 90% confidence interval of the geometric mean ratio of the C_{max} for aspirin in the preliminary study of Study CPH-001 did not fall within the range of 0.80 to 1.25, the C_{max} of aspirin following administration of the LPZ/ASP combination product and coadministration of the single-agent drugs are likely to differ little because the point estimate of the geometric mean ratio was 1.015. The

standard deviation of the mean C_{\max} of aspirin was smaller following administration of the LPZ/ASP combination product than that following coadministration of the single-agent drugs. Variability in the plasma concentration over time of aspirin among individual subjects was likewise smaller following administration of the LPZ/ASP combination product than that following coadministration of the single-agent drugs.

None of the 24 subjects receiving the LPZ/ASP combination product in the preliminary study of Study CPH-001 experienced an adverse event during the study period. Five of the 230 subjects receiving the LPZ/ASP combination product in the main study of Study CPH-001 experienced 6 adverse events, all of which occurred at least 15 days after study drug administration and were found to be causally unrelated to the study drug. Twelve subjects received the LPZ/ASP combination product in a study evaluating the effects of food on the LPZ/ASP combination product. Two subjects experienced 3 adverse events, but a causal relationship with the study drug was ruled out in each case. These findings indicate that patients taking the LPZ/ASP combination product instead of the single-agent drugs together will unlikely encounter any safety problems.

In summary, although the BE of aspirin between the LPZ/ASP combination product and the approved products was not shown, taking the LPZ/ASP combination product instead of the single-agent drugs together is expected to produce clinical efficacy without safety concerns.

PMDA considers as follows:

In developing the LPZ/ASP combination product, the applicant took the strategy of substantiating its therapeutic benefit by showing the BE of lansoprazole and aspirin between the LPZ/ASP combination product and coadministration of previously approved single-agent drugs, but the results of the clinical study (Study CPH-001) and dissolution test performed on the basis of the clinical study failed to show the BE of the LPZ/ASP combination product and coadministration of the single-agent drugs for aspirin, which means that no data were obtained showing that the preventive effect of the LPZ/ASP combination product on thrombosis and embolism is comparable to that of the aspirin products already approved in Japan. The AUC_{0-12} of aspirin following administration of the LPZ/ASP combination product in Study CPH-001, however, satisfied the acceptance criteria for BE. Although the C_{\max} of aspirin following administration of the LPZ/ASP combination product did not satisfy the acceptance criteria for BE, the geometric mean ratio [90% confidence interval] was 1.015 [0.765-1.347], which shows that the pharmacokinetics of aspirin following administration of the LPZ/ASP combination product does not differ substantially from pharmacokinetics following coadministration of the single-agent drugs. It is a common acknowledgement among the societies of medical and pharmaceutical science that the antiplatelet dosage range of low-dose aspirin is to be 75 to 325 mg/day, and both enteric-coated aspirin tablets (with 100 mg of aspirin) and antacid buffered aspirin tablets (with 81 mg of aspirin), with different pharmacokinetic profiles, are approved. Accordingly, aspirin contained in the LPZ/ASP combination product is expected to have the same efficacy and safety as the approved low-dose aspirin

products. PMDA will provide a final decision on the appropriateness of this conclusion after taking account of comments raised in the Expert Discussion.

3.(iii).B.(3) Indication

PMDA considers that the indication of the LPZ/ASP combination product should be as follows because the intended population of the LPZ/ASP combination product must be clearly indicated as patients requiring long-term low-dose aspirin treatment who need to reduce the risk of recurrent gastric or duodenal ulcers.

Indication

Reduction of the risk of thrombosis and embolism formation in patients who have a history of gastric ulcer or duodenal ulcer and who:

- Have angina pectoris (chronic stable angina and unstable angina), myocardial infarction, and ischemic cerebrovascular diseases (transient ischaemic attack [TIA] and cerebral infarction) or
- Underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)

3.(iii).B.(4) Dosage and administration

PMDA concluded as follows:

The following dosage and administration statement for the LPZ/ASP combination product, worded as proposed, is appropriate. This is based on the fact that the dose of aspirin at 100 mg/day is widely used in the Japanese clinical practice for patients requiring low-dose aspirin, and that the dosage of lansoprazole for the “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” is 15 mg orally once daily, and because the LPZ/ASP combination product is considered to have the same efficacy and safety as the coadministration of lansoprazole and low-dose aspirin in Japan [see “3.(iii).B.(2) Aspirin”].

Dosage and administration

The usual adult dosage is one tablet (containing 100 mg of aspirin and 15 mg of lansoprazole) administered orally once daily.

3.(iii).B.(5) Postmarketing considerations

PMDA considers as follows:

There is currently little significance in collecting more information on the LPZ/ASP combination product by conducting new postmarketing surveillance because postmarketing surveillance of lansoprazole for the indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” is ongoing (scheduled to conclude in January 2014), and data on the coadministration of lansoprazole and low-dose aspirin is collected. Although the risk management plan for the LPZ/ASP combination product should be revised as needed to reflect the assessments etc., of the

ongoing postmarketing surveillance of lansoprazole, no written risk management plan need to be submitted because no additional pharmacovigilance plan or additional risk minimization plan is necessary.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.1.2-1). As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Since the therapeutic benefits of coadministering lansoprazole to patients with a history of gastric or duodenal ulcers who require long-term low-dose aspirin were demonstrated when Takepron Capsules 15 and Takepron OD Tablets 15 were approved, the significance of developing the co-formulation of the two active ingredients is considered to be scientifically justified. Based on the submitted data, Takelda Combination Tablets can be expected to have the same efficacy and safety as the coadministration of low-dose aspirin with lansoprazole in patients with a history of gastric or duodenal ulcers requiring long-term treatment with low-dose aspirin. Thus, PMDA has concluded that Takelda Combination Tablets may constitute one treatment option for patients with a history of gastric or duodenal ulcers requiring long-term treatment with low-dose aspirin.

Takelda Combination Tablets may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

January 10, 2014

I. Product Submitted for Registration

[Brand name]	Takelda Combination Tablets
[Non-proprietary name]	Aspirin/Lansoprazole
[Name of applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 27, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the “Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Significance of combining the ingredients

The following conclusion of PMDA was supported by the expert advisors:

The significance of developing the co-formulation of low-dose aspirin and lansoprazole has been demonstrated because Japanese and non-Japanese guidelines recommend PPI coadministration for patients requiring low-dose aspirin who have a history of gastric or duodenal ulcers, and because Takepron Capsules 15 and Takepron OD Tablets 15 were already approved for the indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” based on the results of Japanese clinical studies.

(2) Aspirin

The following conclusion of PMDA was supported by the expert advisors:

In view of the fact that it is a common acknowledgement among the societies of medical and pharmaceutical science that low-dose aspirin as an antiplatelet drug is used at a dosage range of 75 to 325 mg/day, aspirin contained in the LPZ/ASP combination product is expected to have the same efficacy and safety as the approved low-dose aspirin products because a pharmacokinetically different enteric-coated aspirin tablet (with 100 mg of aspirin) and antacid buffered aspirin tablet (with 81 mg of aspirin) were approved, and because Study CPH-001 demonstrated that the AUC₀₋₁₂ of aspirin following administration of the LPZ/ASP combination product satisfied the BE acceptance criteria and that despite the C_{max} of aspirin following administration of the LPZ/ASP combination product failing to meet the BE criteria, the geometric mean ratio [90% CI] was 1.015 [0.765-1.347], showing that the pharmacokinetics of aspirin following administration of the LPZ/ASP combination product does not

differ substantially from pharmacokinetics following coadministration of the single-agent drugs.

(3) Indication

The following conclusion of PMDA was supported by the expert advisors:

The indication of the LPZ/ASP combination product should be as follows because the intended population of the LPZ/ASP combination product is patients requiring long-term low-dose aspirin treatment who need to reduce recurrent gastric or duodenal ulcers.

[Indication]

Reduction of the risk of thrombosis and embolism formation in patients who have a history of gastric ulcer or duodenal ulcer and who:

- Have angina pectoris (chronic stable angina and unstable angina), myocardial infarction, and ischemic cerebrovascular diseases (transient ischaemic attack [TIA] and cerebral infarction) or
- Underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)

(4) Dosage and administration

The following conclusion of PMDA was supported by the expert advisors:

The dosage and administration of the product should be as follows because the dose of 100 mg/day of aspirin is widely used for patients requiring low-dose aspirin in the Japanese clinical practice, because the dosage of lansoprazole for “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” is 15 mg orally once daily, and for other reasons. It was concluded that the composition of the product should be described as “100 mg of aspirin and 15mg of lansoprazole” and that the dosage and administration section should be written as follows because the product is a combination drug to be administered to patients requiring long-term treatment with low-dose aspirin.

[Dosage and administration]

The usual adult dosage is one tablet (containing 100 mg of aspirin and 15 mg of lansoprazole) administered orally once daily.

(5) Postmarketing considerations

The following conclusion of PMDA was supported by the expert advisors:

There is currently little significance in collecting more information on the product by conducting new postmarketing surveillance because safety data on the coadministration of lansoprazole and low-dose aspirin is collected in a use-results survey of lansoprazole for the indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin,” which is scheduled to be completed in January 2014.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration statement as shown below. The re-examination period for the product is the remainder of the re-examination period for the lansoprazole indication of “reduction of the risk of recurrent gastric or duodenal ulcers associated with low-dose aspirin” (i.e., to July 22, 2014).

[Indication] Reduction of the risk of thrombosis and embolism formation in patients who have a history of gastric ulcer or duodenal ulcer and who:

- Have angina pectoris (chronic stable angina and unstable angina), myocardial infarction, and ischemic cerebrovascular diseases (transient ischemic attack [TIA] and cerebral infarction) or
- Underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)

[Dosage and administration]

The usual adult dosage is one tablet (containing 100 mg of aspirin and 15 mg of lansoprazole) administered orally once daily.