

## Report on the Deliberation Results

May 14, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau  
Ministry of Health, Labour and Welfare

[Brand name]	Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, Talion OD Tablets 10 mg
[Non-proprietary name]	Bepotastine Besilate (JAN*)
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	May 30, 2014

### [Results of deliberation]

In the meeting held on April 24, 2015, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is 4 years.

### [Condition for approval]

The applicant is required to develop and appropriately implement a risk management plan.

*\*Japanese Accepted Name (modified INN)*

## Review Report

April 16, 2015  
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]	Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, Talion OD Tablets 10 mg
[Non-proprietary name]	Bepotastine Besilate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	May 30, 2014
[Dosage form/Strength]	Film-coated tablet or orally disintegrating tablet: Each tablet contains 5 or 10 mg of Bepotastine Besilate
[Application classification]	Prescription drug, (6) Drug with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

*This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.*

## Review Results

April 16, 2015

[Brand name] Talion Tablets 5 mg,  
Talion Tablets 10 mg,  
Talion OD Tablets 5 mg,  
Talion OD Tablets 10 mg  
[Non-proprietary name] Bepotastine Besilate  
[Applicant] Mitsubishi Tanabe Pharma Corporation  
[Date of application] May 30, 2014

### [Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) considers that the efficacy of the product in children aged  $\geq 7$  years with allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, cutaneous pruritus) has been demonstrated and its safety is acceptable in view of its observed benefits. The occurrence of neuropsychiatric adverse events needs to be further investigated via post-marketing surveillance.

As a result of its review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following condition.

### [Indication]

#### Adults

Allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, prurigo, cutaneous pruritus)

#### Children

Allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, cutaneous pruritus)

(Underline denotes the text added in this application.)

### [Dosage and administration]

#### Adults

The usual adult dosage is 10 mg of bepotastine besilate administered orally twice daily. The dose may be adjusted according to the patient's age and symptoms.

#### Children

The usual dosage for children aged  $\geq 7$  years is 10 mg of bepotastine besilate administered orally twice daily.

(Underline denotes the text added in this application.)

### [Condition for approval]

The applicant is required to develop and appropriately implement a risk management plan.

## Review Report (1)

February 20, 2015

### I. Product Submitted for Registration

[Brand name]	Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, Talion OD Tablets 10 mg
[Non-proprietary name]	Bepotastine Besilate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	May 30, 2014
[Dosage form/Strength]	Film-coated tablet or orally disintegrating tablet: Each tablet contains 5 or 10 mg of Bepotastine Besilate
[Proposed indication]	<u>Adults</u> Allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, prurigo, cutaneous pruritus) <u>Children</u> <u>Allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, cutaneous pruritus)</u> (Underline denotes the text added in this application.)
[Proposed dosage and administration]	<u>Adults</u> The usual adult dosage is 10 mg of bepotastine besilate administered orally twice daily. The dose may be adjusted according to the patient's age and symptoms. <u>Children</u> <u>The usual dosage for children aged <math>\geq 7</math> years is 10 mg of bepotastine besilate administered orally twice daily.</u> (Underline denotes the text added in this application.)

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

Since this application seeks approval of an additional dosage for children aged  $\geq 7$  years, pharmacology data have not been submitted as a part of "Data relating to quality" or "Non-clinical data."

#### 1. Origin or history of discovery, use in foreign countries, and other information

Bepotastine besilate, the active ingredient of Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, and Talion OD Tablets 10 mg (hereinafter collectively referred to as Talion), is a histamine H<sub>1</sub> receptor antagonist that was discovered by Ube Industries, Ltd. and co-developed by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. (currently Mitsubishi Tanabe Pharma Corporation).

In Japan, Talion Tablets 5 mg and Talion Tablets 10 mg<sup>1</sup> were approved for use at 10 mg twice daily in adults for the indications of "allergic rhinitis" in July 2000 and "urticaria and pruritus associated with skin disorders (eczema/dermatitis, prurigo, and cutaneous pruritus)" in January 2002. Talion OD Tablets 5 mg and Talion OD Tablets 10 mg, which are orally disintegrating tablets, were approved in March 2007 for the same indications and the same dosage and administration as those of Talion Tablets.

In foreign countries, as of February 2015, the oral formulations containing bepotastine besilate as an active ingredient are approved in Korea, China, and Indonesia for use in adults for the indications of

<sup>1</sup> Brand names of Talion Tablets 5 and Talion Tablets 10 were changed to Talion Tablets 5 mg and Talion Tablets 10 mg, respectively, in March 2008 through the new application for replacement of license to change brand name.

allergic rhinitis, urticaria, or pruritus associated with skin disorders, but the dosage and administration for children is not approved in any countries.

In Japan, the clinical development of Talion in children was initiated in [REDACTED] 20[REDACTED]. Based on the results from Japanese clinical studies, a partial change application of an additional dosage for children has been submitted.

## 2. Non-clinical data

### 2.(i) Summary of pharmacology studies

#### 2.(i).A Summary of the submitted data

Because age was considered to have no effect on the histamine H<sub>1</sub> receptor antagonism of Bepotastine Besilate (hereinafter referred to as bepotastine besilate), no new pharmacology study has been conducted for the purpose of this application.

### 2.(ii) Summary of pharmacokinetic studies

#### 2.(ii).A Summary of the submitted data

The applicant submitted the evaluation data on absorption, distribution, metabolism, and excretion, resulting from studies in which <sup>14</sup>C-bepotastine besilate was orally or intravenously administered to juvenile (25 days of age) and adult (7-8 months of age) dogs. Radioactivity levels in biological samples were measured by liquid scintillation counter (the detection limit is 2-fold the background radioactivity), or by high performance liquid chromatography (HPLC) (the detection limit is 3-fold the background radioactivity).

Unless otherwise specified, pharmacokinetic parameters are expressed as mean or mean ± standard deviation (SD).

#### 2.(ii).A.(1) Absorption

##### 2.(ii).A.(1).1 Single oral and intravenous dose study in juvenile and adult dogs (4.2.2.2-1)

Table 1 shows the pharmacokinetic parameters of plasma radioactivity following a single oral or intravenous dose of <sup>14</sup>C-bepotastine 0.3 mg/kg in juvenile dogs (n = 3 males/group) under fed conditions and in adult dogs (n = 3 males) under fasted conditions. C<sub>max</sub>, AUC<sub>inf</sub>, and CL<sub>(oral)</sub> following a single oral dose of <sup>14</sup>C-bepotastine in juvenile dogs were 0.52, 0.70, and 1.54-fold those in adult dogs, respectively. C<sub>0</sub>, AUC<sub>inf</sub>, and CL<sub>total</sub> following a single intravenous dose in juvenile dogs were 0.61, 0.86, and 1.19-fold those in adult dogs, respectively.

**Table 1. Pharmacokinetic parameters following a single oral or intravenous dose of <sup>14</sup>C-bepotastine besilate in juvenile and adults dogs**

	Species	No. of animals	Dose (mg/kg)	C <sub>max</sub> (ng eq./mL)	T <sub>max</sub> (h)	AUC <sub>inf</sub> (ng eq.·h/mL)	t <sub>1/2</sub> (h)	CL (mL/h/kg)	V <sub>0</sub> (mL/kg)
Oral	Juvenile dog (fed)	3 males	0.3	118.7 ± 14.0	3.0 ± 0.0	1.3 ± 0.5	12.4 ± 4.9	172.6 ± 49.5	-
	Adult dog (fasted)	3 males		227.0 ± 14.8	0.7 ± 0.3	1.9 ± 0.0	9.2 ± 0.4	112.3 ± 1.5	-
Intravenous	Juvenile dog	3 males		376.4 ± 23.8 <sup>b)</sup>	-	1.5 ± 0.3	7.7 ± 1.2	147.1 ± 31.1	559.8 ± 37.8
	Adult dog	3 males <sup>a)</sup>		615.9 ± 132.0 <sup>b)</sup>	-	1.7 ± 0.1	8.6 ± 0.6	123.1 ± 3.8	359.9 ± 89.2

Mean ± SD

C<sub>max</sub>, Maximum plasma concentration; T<sub>max</sub>, Time to maximum plasma concentration; AUC, Area under the plasma concentration-time curve; t<sub>1/2</sub>, Elimination half-life; CL, Plasma clearance; V<sub>0</sub>, Initial volume of distribution

a) The same animals in the oral dose evaluation were used for intravenous dose evaluation.

b) C<sub>0</sub>.

The applicant's explanation:

The observed difference in exposure between juvenile and adult dogs might have been caused by a possible difference in V<sub>0</sub> following intravenous administration since the plasma-interstitial fluid volume in juvenile dogs (370 mL/kg) was greater than that in adult dogs (176 mL/kg). The inconsistent feeding conditions used in the evaluation of oral administration might have been another factor.

## **2.(ii).A.(2) Distribution**

### **2.(ii).A.(2).1 Single oral dose study in juvenile and adult dogs (4.2.2.3-1)**

Following a single oral dose of <sup>14</sup>C-bepotastine besilate 0.3 mg/kg in juvenile dogs and adult dogs (n = 3 males each), the radioactivity level in juvenile dogs was highest in the liver, followed in descending order by the kidney, spleen, and pancreas. The radioactivity level in adult dogs was highest in the large intestine, followed in descending order by the kidney, liver, and pancreas. Although radioactivity levels in fat (excluding gastrointestinal tract) and bone marrow tended to be higher in juvenile dogs than in adult dogs, no substantial difference was observed in other tissues.

The applicant's discussion:

Adverse events associated with bepotastine besilate in bone marrow or fat tissues are unlikely to occur because no toxicological changes in these organs were observed in the 4-week repeated oral dose toxicity study in juvenile dogs.

### **2.(ii).A.(2).2 *In vitro* plasma protein binding and distribution in blood cells in juvenile and adult dogs (4.2.2.3-2)**

When <sup>14</sup>C-bepotastine besilate was added at concentrations of 0.1, 0.3, and 3 µg eq./mL to plasma of juvenile and adult dogs, plasma protein binding was 45.9% to 48.9% in juvenile dogs and 59.5% to 61.5% in adult dogs. Total serum protein and albumin levels seen in the 4-week repeated oral dose toxicity study in adult dogs (5.6 and 3.1 g/dL, respectively) were approximately 1.4-fold those in juvenile dogs (3.9 and 2.2 g/dL, respectively). Based on the above, the applicant explained that the observed difference in plasma protein binding between juvenile and adult dogs would be due to the difference in total protein levels.

When <sup>14</sup>C-bepotastine besilate was added at concentrations of 0.1, 0.3, and 3 µg eq./mL to blood of juvenile and adult dogs, the blood/plasma radioactivity ratio was 0.95 to 0.97 in juvenile dogs and 0.92 to 0.93 in adult dogs.

## **2.(ii).A.(3) Metabolism**

### **2.(ii).A.(3).1 Plasma and urinary metabolites in juvenile and adult dogs (4.2.2.4-1)**

At 0.5, 3, and 6 hours after a single oral dose of <sup>14</sup>C-bepotastine besilate 0.3 mg/kg in juvenile and adult dogs (n = 3 males each), 97.4% to 99.2% and 95.3% to 98.2%, respectively, of the total radioactivity recovered in plasma were unchanged bepotastine, and metabolites were hardly detected. In addition, unchanged bepotastine up to 24 hours after dosing accounted for 93.3% and 94.2% of the urinary radioactivity in juvenile and adult dogs, respectively, and metabolites were hardly detected in urine similarly.

## **2.(ii).A.(4) Excretion**

### **2.(ii).A.(4).1 Urinary and fecal excretions in juvenile and adult dogs (4.2.2.5-1)**

Following a single oral dose of <sup>14</sup>C-bepotastine besilate 0.3 mg/kg in juvenile and adult dogs (n = 3 males each), the urinary and fecal excretion rates (percentage of administered radioactivity recovered) up to 24 hours after dosing were 76.7% and 14.3%, respectively, in juvenile dogs and 73.6% and 11.9%, respectively, in adult dogs.

## **2.(ii).B Outline of the review by PMDA**

Based on the submitted data and the applicant's discussion, PMDA considered that no particular problems have been suggested with the pharmacokinetic evaluation submitted in this application.

## **2.(iii) Summary of toxicology studies**

### **2.(iii).A Summary of the submitted data**

The applicant submitted the toxicity data of bepotastine besilate resulting from single and repeated oral dose toxicity studies in juvenile rats and juvenile dogs.

## **2.(iii).A.(1) Single-dose toxicity**

### **2.(iii).A.(1).1 Single oral dose toxicity study in juvenile rats (4.2.3.1-1)**

A single oral dose of bepotastine besilate 0 (vehicle, 0.5% methylcellulose 1500 solution), 500, 1000, or 2000 mg/kg was administered to juvenile male and female SD rats (4 days of age). As a result, 3 of 6

males and 6 of 6 females in the 1000 mg/kg group died within 5 days post-dose, and 6 of 6 males and 6 of 6 females in the 2000 mg/kg group died within 3 hours post-dose. Changes in clinical signs such as decreased activity, pale skin, and respiratory effect were observed in animals of the  $\geq 1000$  mg/kg groups, and transient reduced body weight gain or decreased body weight was observed in surviving animals of the  $\geq 500$  mg/kg groups. Necropsy findings of dead animals included hyperemia, bleeding, edema, or neutrophilic inflammatory cell infiltration in the lamina propria or muscular layer of the glandular stomach. Some of the dead animals showed bleeding, congestion, or edema in the lungs. Based on the above, the approximate lethal dose in this study was determined to be 1000 mg/kg.

#### **2.(iii).A.(1).2) Single oral dose toxicity study in juvenile dogs (4.2.3.1-2)**

A single oral dose of bepotastine besilate 0 (vehicle), 500, 1000, or 2000 mg/kg was administered to juvenile male and female beagle dogs (21 days of age). As a result, 1 of 2 females in the 2000 mg/kg group died 2 days post-dose. Decreased activity, vomiting, or loose stool was observed in animals of the  $\geq 1000$  mg/kg groups, and prone position and hypothermia were also observed in some of the dead animals, but no apparent effects were observed on body weight. Necropsy findings of dead animals included mild bleeding in the lungs. Based on the above, the approximate lethal dose in this study was determined to be 2000 mg/kg.

#### **2.(iii).A.(2) Repeat-dose toxicity**

The main toxicological findings seen in the repeat-dose toxicity studies in juvenile animals included elevated activity of liver drug-metabolizing enzymes, and mucosal epithelial hyperplasia of the bladder was also observed in dogs. However, all of these findings were also observed in adult animals, and there were no toxicological findings that were unique to juvenile animals. Compared to the  $C_{max}$  (92.0 ng/mL) after 1 week of repeated oral dose of bepotastine besilate 20 mg/day in Japanese pediatric patients aged 7 to 15 years with perennial allergic rhinitis, plasma concentrations of unchanged bepotastine (2.00-2.20  $\mu\text{g/mL}$ ) at 1 hour post-dose at the no observed adverse effect level (NOAEL) determined in the 4-week repeated oral dose toxicity study in juvenile rats were approximately 22- to 24-fold, and  $C_{max}$  (69.0 to 70.3  $\mu\text{g/mL}$ ) at the NOAEL determined in the 4-week repeated oral dose toxicity study in juvenile dogs was approximately 750- to 764-fold.

#### **2.(iii).A.(2).1) Preliminary 2-week repeated oral dose toxicity study in juvenile rats (4.2.3.2-1)**

Repeated oral doses of bepotastine besilate 0 (vehicle), 60, 200, or 600 mg/kg/day were administered to juvenile male and female SD rats (4 days of age) for 2 weeks. Findings observed in animals in the 600 mg/kg/day group included deaths (3 of 6 males, 2 of 6 females), mydriasis, reduced body weight gain, increases in red blood cell count, hematocrit value, total bilirubin levels, and potassium levels, and elevated activity of aspartate aminotransferase (AST). An increase in the relative weight of the liver and centrilobular hepatocellular fatty changes were observed in animals in the  $\geq 200$  mg/kg/day groups. Based on the above, the NOAEL in this study was determined to be 60 mg/kg/day.

#### **2.(iii).A.(2).2) Four-week repeated oral dose toxicity study in juvenile rats (4.2.3.2-3)**

Repeated oral doses of bepotastine besilate 0 (vehicle), 20, 60, or 200 mg/kg/day were administered to juvenile male and female SD rats (4 days of age) for 4 weeks. No bepotastine besilate -related deaths were observed, while reduced body weight gain was observed in animals in the 200 mg/kg/day group. Findings related to activity of liver drug-metabolizing enzymes included elevated activity of aminopyrine N-demethylase in animals in the  $\geq 60$  mg/kg/day groups, a trend toward increased content of cytochrome P-450 in males in the  $\geq 60$  mg/kg/day groups and females in the 200 mg/kg/day group, and a trend toward elevated activity of aniline hydroxylase in males in the  $\geq 60$  mg/kg/day groups. An increase in the relative weight of the liver was observed in males in the  $\geq 60$  mg/kg/day groups and females in the 200 mg/kg/day group. Centrilobular hepatocellular hypertrophy was observed in 1 of 12 males and 1 of 12 females in the 200 mg/kg/day group. These changes in the liver were considered to be adaptive responses caused by the elevated activity of drug-metabolizing enzymes because the above findings improved or resolved after a recovery, and therefore were reversible. Based on the above, the NOAEL in this study was determined to be 20 mg/kg/day.

#### **2.(iii).A.(2).3) Preliminary 2-week repeated oral dose toxicity study in juvenile dogs (4.2.3.2-2)**

Repeated oral doses of bepotastine besilate 0 (vehicle), 60, 200, or 600 mg/kg/day were administered to juvenile male and female beagle dogs (21 days of age) for 2 weeks. No deaths were observed, but

salivation, an increase in urine volume, and an increase in the relative weight of the liver were observed in animals in the 600 mg/kg/day group. Based on the above, the NOAEL in this study was determined to be 200 mg/kg/day.

**2.(iii).A.(2).4) Four-week repeated oral dose toxicity study in juvenile dogs (4.2.3.2-4)**

Repeated oral doses of bepotastine besilate 0 (vehicle), 60, 200, or 600 mg/kg/day were administered to juvenile male and female beagle dogs (21 days of age) for 4 weeks. Neither bepotastine besilate-related deaths nor abnormal findings in clinical signs, body weight, ophthalmology, or laboratory tests were observed. Findings related to activity of liver drug-metabolizing enzymes included mildly increased content of cytochrome P-450, and mildly elevated activities of aminopyrine N-demethylase and aniline hydroxylase in males of the 600 mg/kg/day group, but these findings were reversible. Reversible and mild mucosal epithelial hyperplasia of the bladder was observed in 1 of 3 females of the 600 mg/kg/day group. Based on the above, the NOAEL in this study was determined to be 200 mg/kg/day.

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

Based on the submitted study data and on the non-clinical toxicity study data submitted with initial application for bepotastine besilate, PMDA considered that there are no new toxicological concerns about the use of bepotastine besilate in children because no substantial differences exist in the toxicological findings between adult and juvenile animals and no toxic changes that were unique to juvenile animals have been observed.

**3. Clinical data**

**3.(i) Summary of biopharmaceutical studies and clinical pharmacology studies**

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

The applicant submitted evaluation data, resulting from a Japanese phase III study in pediatric patients 7 to 15 years of age with perennial allergic rhinitis (5.3.5.1-1, Study TAU-284-17), a Japanese phase III study in pediatric patients 7 to 15 years of age with atopic dermatitis (5.3.5.1-3, Study TAU-284-19), and a population pharmacokinetic analysis (5.3.3.5-1). Plasma concentrations of unchanged bepotastine were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with lower limit of quantitation of 0.2 ng/mL.

Unless otherwise specified, the doses of Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, and Talion OD Tablets 10 mg (hereinafter collectively referred to as Talion) are expressed as bepotastine besilate equivalent, and pharmacokinetic parameters are expressed as mean or mean ± SD.

**3.(i).A.(1) Japanese phase III study in pediatric patients with perennial allergic rhinitis (5.3.5.1-1, Study TAU-284-17 [██████ to ██████ 2011])**

A randomized, double-blind, parallel-group, placebo-controlled study was conducted in 490 pediatric patients aged 7 to 15 years with perennial allergic rhinitis to evaluate the pharmacokinetics of Talion (112 subjects were analyzed for pharmacokinetics). Table 2 shows plasma concentrations of unchanged bepotastine following oral administration of Talion 5 or 10 mg twice daily. Plasma concentrations of unchanged bepotastine increased with increasing dose and those at 9 to 15 hours post-dose, which were considered to be trough concentrations, were comparable between Week 1 and Week 2.

**Table 2. Plasma concentrations of unchanged bepotastine (ng/mL) following oral administration of Talion 5 or 10 mg twice daily in pediatric patients with perennial allergic rhinitis**

	No. of subjects	1-3 hours post-dose		9-15 hours post-dose	
		Week 1		Week 1	Week 2 weeks
5 mg twice daily	50	54.7 ± 31.1		3.7 ± 1.8	5.4 ± 8.4
10 mg twice daily	62	92.0 ± 56.1		7.9 ± 4.6	7.3 ± 3.9

Mean ± SD

**3.(i).A.(2) Japanese phase III study in pediatric patients with atopic dermatitis (5.3.5.1-3, Study TAU-284-19 [March to November 2013])**

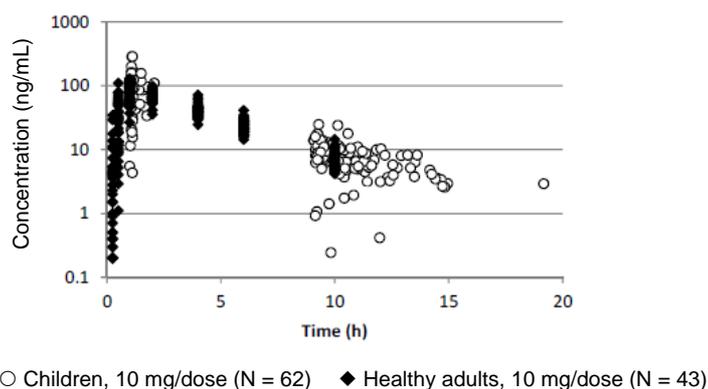
A randomized, double-blind, parallel-group study was conducted in 303 pediatric patients aged 7 to 15 years with atopic dermatitis to evaluate the pharmacokinetics of bepotastine (148 subjects analyzed for

pharmacokinetics). After 2 weeks of oral administration of Talion 10 mg twice daily, the trough plasma concentration of unchanged bepotastine (9-15 hours post-dose) was  $8.5 \pm 10.3$  ng/mL (148 subjects).

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

The applicant's explanation on the proposed dosage and administration of Talion for children aged 7 to 15 years from a pharmacokinetic viewpoint:

Data from Study TAU-284-17, conducted in pediatric patients with perennial allergic rhinitis, and Study TAU-284FD-01, conducted in healthy adult subjects, were used to compare plasma concentrations of unchanged bepotastine between adults and children aged 7 to 15 years who received Talion 10 mg/dose (approved dose for adults). The results showed that plasma concentrations of unchanged bepotastine were similar between pediatric patients with perennial allergic rhinitis and healthy adult subjects as shown in Figure 1.



**Figure 1. Plasma concentration of unchanged bepotastine over time following Talion 10 mg administration in pediatric patients with perennial allergic rhinitis and in healthy adult subjects (Data for pediatric patients with perennial allergic rhinitis from Study TAU-284-17, data for healthy adult subjects from Study TAU-284FD-01)**

[REDACTED]

The pharmacokinetic parameters in children (by body weight) and adult subjects are shown in Table 3. The plasma  $C_{min}$  of unchanged bepotastine was similar between healthy adult subjects and children, while  $C_{max}$  and  $AUC_{0-12}$  tended to be higher in children with lower body weight; data suggested that  $C_{max}$  and  $AUC_{0-12}$  in children aged around 7 years with body weight<sup>4</sup> (20 kg) may exceed those in healthy adult subjects.

**Table 3. Pharmacokinetic parameters in healthy adult subjects and children (by body weight) estimated from population pharmacokinetic analysis**

	$C_{max}$ (ng/mL)	$C_{min}$ (ng/mL)	$AUC_{0-12}$ (ng·h/mL)
Healthy adult subjects	86.9 (40.7, 175.5)	3.6 (0.5, 10.3)	356 (211, 600)
Children (20 kg body weight)	175.6 (80.0, 358.9)	4.3 (0.8, 14.6)	656 (388, 1114)
Children (40 kg body weight)	86.8 (41.3, 174.9)	4.8 (1.2, 12.6)	378 (224, 637)
Children (60 kg body weight)	57.5 (27.9, 115.0)	4.7 (1.2, 11.3)	271 (161, 456)

Median (2.5 percentile, 97.5 percentile)

[REDACTED]

<sup>3</sup> A model that was based on the 1-compartment model with 4 transit compartments and first-order absorption, in which body weight was included as a covariate for pediatric Vc/F and for pediatric CL/F.

<sup>4</sup> Average body weight in boys and girls by age: 7 years, 23.9 kg and 23.5 kg; 12 years, 43.9 kg and 43.7 kg; 15 years, 58.9 kg and 51.4 kg, respectively (*Annual Report of School Health Statistics Research 2013*).

Although the estimated  $C_{max}$  and AUC in children around 7 years of age tended to be higher than those in healthy adult subjects (Table 3), no safety problems were indicated from the following evaluations.

Safety in 11 pediatric patients with perennial allergic rhinitis was evaluated in whom plasma concentrations of unchanged bepotastine (136.2-284.6 ng/mL) exceeded the highest  $C_{max}$  (128.5 ng/mL) observed among 42 healthy adult subjects who received 10 mg of Talion. As a result, 1 subject experienced pyrexia and epistaxis, but both events were mild in severity and a causal relationship to Talion was ruled out.

In addition, the incidence of adverse events by age in subjects in the Talion 20 mg/day groups based on combined data from Studies TAU-284-17, TAU-284-18, TAU-284-19, and TAU-284-20 was 27.2% (61 of 224 subjects) in subjects aged <10 years, 19.2% (44 of 229 subjects) in subjects aged  $\geq 10$  and <13 years, and 16.7% (27 of 162 subjects) in subjects aged  $\geq 13$  years, indicating a trend toward a higher incidence in children aged <10 years. Adverse events, which were reported by  $\geq 3\%$  of children aged <10 years and occurred with  $\geq 2$ -fold the incidence in other age groups, were nasopharyngitis, pharyngitis, and epistaxis, and a causal relationship to Talion was ruled out for all of them. These events were considered to be incidental events due to seasonal variation or events associated with the primary disease. Moreover, an evaluation in smaller age ranges (7, 8, and 9 years) in children aged <10 years revealed that the incidence of adverse events reported from these studies was 15.4% to 66.7% in subjects aged 7 years (3-31 subjects), 34.5% to 66.7% in subjects aged 8 years (6-29 subjects), and 14.0% to 83.3% in subjects aged 9 years (6-43 subjects), indicating no differences. Thus, no effects of age were observed on the incidence of adverse events.

Though retrospective, an investigation was furthermore performed on the incidence of adverse drug reactions in 1316 pediatric patients based on the specified drug use-results survey of children treated with Talion (survey period, July 2001 to June 2002). The incidence was 0% (0 of 27 patients) in patients aged <7 years, 1.7% (5 of 300 patients) in patients aged  $\geq 7$  and <10 years, 0.7% (4 of 564 patients) in patients aged  $\geq 10$  and <13 years, and 1.2% (5 of 425 patients) in patients aged  $\geq 13$  and <15 years, indicating no trend toward a particularly higher incidence of adverse drug reactions with decreasing age.

Based on the above, plasma concentrations of unchanged bepotastine in children aged 7 to 15 years who received 10 mg/dose of bepotastine, the dose approved for adults, were generally similar to those in adults receiving the same dose, and although the exposure may be higher in children around 7 years of age than in adults, there were no safety problems. Therefore, a dosage of Talion 10 mg twice daily, the same dosage for adults, should be selected for children aged 7 to 15 years.

PMDA's view:

Taking account of the submitted clinical pharmacology study data and the applicant's discussion, there are no particular pharmacokinetic concerns with the dosage regimen of Talion 10 mg twice daily for children aged 7 to 15 years, but conclusion on the appropriate dose regimen should be based on the clinical study data [see "3.(ii) Summary of clinical efficacy and safety"].

### **3.(ii) Summary of clinical efficacy and safety**

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

The applicant submitted the efficacy and safety evaluation data resulting from 2 Japanese phase III studies (Studies TAU-284-17 [5.3.5.1-1] and TAU-284-20 [5.3.5.1-2]), a Japanese long-term treatment study (Study TAU-284-18 [5.3.5.2-1]) in pediatric patients with perennial allergic rhinitis, and a Japanese phase III study in pediatric patients with atopic dermatitis (Study TAU-284-19 [5.3.5.1-3]). The dose of Talion is expressed as bepotastine besilate equivalent.

**3.(ii).A.(1) Japanese phase III study in pediatric patients with perennial allergic rhinitis (5.3.5.1-1, Study TAU-284-17 [██████ to ██████ 2011])**

A randomized, double-blind, parallel-group, placebo-controlled study was conducted to evaluate the efficacy and safety of Talion in pediatric patients aged  $\geq 7$  and  $\leq 15$  years with perennial allergic rhinitis<sup>5</sup> (target sample size of 450 [150 per group]).

Talion 5 or 10 mg or placebo was to be administered orally twice daily after morning and evening meals (or at bedtime) for 2 weeks.

All of the 490 randomized<sup>6</sup> subjects (161 in the 10 mg/day group, 166 in the 20 mg/day group, 163 in the placebo group) were included in the Full Analysis Set (FAS), and the safety and efficacy analysis sets. The study was discontinued in a total of 1 of 161 subjects (0.6%) in the 10 mg/day group, 1 of 166 subjects (0.6%) in the 20 mg/day group, and 4 of 163 subjects (2.5%) in the placebo group, and the main reasons included adverse events (1 of 166 subjects [0.6%] in the 20 mg/day group, 1 of 163 subjects [0.6%] in the placebo group), etc.

The primary efficacy endpoint was the change from baseline to the final assessment in the total score of 3 major nasal symptoms<sup>7</sup> (paroxysmal sneezing, nasal discharge, nasal congestion), which is shown in Table 4. No statistically significant differences were found in the pairwise comparison between the 10 mg/day or 20 mg/day group and the placebo group, and therefore the superiority of Talion over placebo was not demonstrated.

**Table 4. Change from baseline to final assessment in the total score of 3 major nasal symptoms (FAS)**

	Talion 10 mg/day	Talion 20 mg/day	Placebo
Baseline <sup>a)</sup>	5.6 ± 1.3 (161)	5.5 ± 1.2 (166)	5.6 ± 1.3 (163)
Final assessment <sup>b)</sup>	4.7 ± 1.9 (161)	4.6 ± 1.7 (166)	4.9 ± 1.9 (162)
Change from baseline	-0.8 ± 1.5 (161)	-0.9 ± 1.7 (166)	-0.7 ± 1.6 (162)
Difference from the placebo group [95% confidence interval (CI)], <sup>c)</sup> P value <sup>c),d)</sup>	-0.14 [-0.49, 0.20]	-0.22 [-0.56, 0.12] P = 0.211	

Mean ± SD (number of subjects)

a) Average of the last 4 day's data in the run-in period (from the next day of enrollment to the day before randomization)

b) Average of the last 4 day's data in the treatment period from the assessment day of Week 1 to the day before the final assessment (for subjects with missing data, average of the last 4 day's data from the next day of enrollment to the day before the assessment day of Week 1 was adopted)

c) Analysis of the covariance (ANCOVA) model with the treatment group and the baseline value as explanatory variables

d) Multiplicity was controlled by step-down closed testing from the highest dose.

Adverse events were reported by 30 of 161 subjects (18.6%) in the Talion 10 mg/day group, 25 of 166 subjects (15.1%) in the Talion 20 mg/day group, and 36 of 163 subjects (22.1%) in the placebo group. Adverse events reported by  $\geq 2\%$  of subjects in any group included nasopharyngitis (8 of 161 subjects [5.0%] in the 10 mg/day group, 3 of 166 subjects [1.8%] in the 20 mg/day group, 11 of 163 subjects [6.7%] in the placebo group), pharyngitis (5 of 161 subjects [3.1%] in the 10 mg/day group, 2 of 166 subjects [1.2%] in the 20 mg/day group, 4 of 163 subjects [2.5%] in the placebo group), and epistaxis (5 of 161 subjects [3.1%] in the 10 mg/day group, 4 of 166 subjects [2.4%] in the 20 mg/day group). There were no deaths or serious adverse events. Adverse events leading to discontinuation included urticaria (1 of 166 subjects [0.6%]) in the 20 mg/day group and constipation (1 of 163 subjects [0.6%]) in the placebo group. Both events were moderate in severity and a causal relationship to the study drug could not be ruled out, but the outcomes were reported as "recovered/resolved."

<sup>5</sup> Key inclusion criteria at enrollment: Patients with (a) positive result in skin testing (intracutaneous or scratch testing) or in serum specific IgE antibody quantitation for house dusts or mites; (b) positive result in nasal provocation test or eosinophil count test in nasal fluid; and (c) body weight of  $\geq 20$  kg, according to the diagnostic classification for allergy described in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2009*,

<sup>6</sup> After placebo was administered orally twice daily in a single-blind manner in the 1 week run-in period (526 subjects), subjects were randomized if their averages of the nasal discharge score and total score of 3 major nasal symptoms were  $\geq 2$  and  $\geq 4$ , respectively.

<sup>7</sup> The total score obtained according to the severity criteria described in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2009* by summing each score of paroxysmal sneezing, nasal discharge, and nasal congestion ranging from 0 to 3 points, based on the nasal allergy diary journalized by each subject or his/her legally acceptable representative. The averages of the total score and individual nasal symptom scores were obtained using only data on a day when all scores of the 3 major nasal symptoms were available. When the investigator (or sub-investigator) assessed that there was an event with an impact on the nasal symptom evaluation, data on that day were excluded.

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were reported by 2 of 161 subjects (1.2%) in the Talion 10 mg/day group, 5 of 166 subjects (3.0%) in the Talion 20 mg/day group, and 7 of 163 subjects (4.3%) in the placebo group.

### 3.(ii).A.(2) Japanese phase III study in pediatric patients with perennial allergic rhinitis (5.3.5.1-2, Study TAU-284-20 [April to December 2013])

A randomized, double-blind, parallel-group, placebo-controlled study was conducted to evaluate the efficacy and safety of Talion in pediatric patients aged  $\geq 7$  and  $\leq 15$  years with perennial allergic rhinitis<sup>8</sup> (target sample size of 450 [225 per group]).

Talion 10 mg or placebo was to be administered orally twice daily after morning and evening meals (or at bedtime) for 2 weeks.

Of 473 randomized<sup>9</sup> subjects (240 in the 20 mg/day group, 233 in the placebo group), 472 subjects treated with the study drug (240s in the 20 mg/day group, 232 in the placebo group) were included in the FAS and the safety and efficacy analysis sets. The study was discontinued in a total of 3 of 240 subjects (1.3%) in the 20 mg/day group and 1 of 233 subjects (0.4%) in the placebo group, and the main reasons included consent withdrawal (2 of 240 subjects [0.8%] in the 20 mg/day group), etc.

The primary efficacy endpoint was the change from baseline to final assessment in the total score of 3 major nasal symptoms<sup>10</sup> (paroxysmal sneezing, nasal discharge, nasal congestion), and is shown in Table 5. Statistically significant differences were found in the pairwise comparison between the 20 mg/day and placebo groups, and therefore the superiority of Talion 20 mg/day over placebo has been demonstrated.

**Table 5. Change from baseline to final assessment in the total score of 3 major nasal symptoms (FAS)**

	Talion 20 mg/day	Placebo
Baseline <sup>a)</sup>	6.533 ± 1.194 (240)	6.383 ± 1.128 (232)
Final assessment <sup>b)</sup>	4.946 ± 1.654 (239)	5.280 ± 1.830 (232)
Change from baseline	-1.587 ± 1.332 (239)	-1.102 ± 1.462 (232)
Difference from the placebo group [95% CI], <sup>c)</sup> P value <sup>c)</sup>	-0.470 [-0.723, -0.217] P < 0.001	

Mean ± SD (number of subjects)

a) Average of the last 4 day's data in the run-in period (from the next day of enrollment to the day before randomization)

b) Average of the last 4 day's data in the treatment period from the assessment day of Week 1 to the day before the final assessment (for subjects with missing data, average of the last 4 day's data from the next day of enrollment to the day before assessment day of Week 1 was adopted)

c) ANCOVA model with the treatment group and the baseline value as explanatory variables

Adverse events were reported by 41 of 240 subjects (17.1%) in the Talion 20 mg/day group and 40 of 232 subjects (17.2%) in the placebo group, and adverse events reported by  $\geq 2\%$  of subjects in either group included pharyngitis (10 of 240 subjects [4.2%] in the 20 mg/day group, 6 of 232 subjects [2.6%] in the placebo group) and nasopharyngitis (7 of 240 subjects [2.9%] in the 20 mg/day group, 9 of 232 subjects [3.9%] in the placebo group). There were no deaths or serious adverse events. Adverse event leading to discontinuation included pseudocroup (1 of 240 subjects [0.4%]) in the 20 mg/day group; this event was moderate in severity and a causal relationship to the study drug was ruled out, and the outcome was reported as "recovered/resolved."

<sup>8</sup> Key inclusion criteria at enrollment: Patients with (a) a positive result in skin testing (intracutaneous or scratch testing) or in serum specific IgE antibody quantitation for house dusts or mites; and (b) positive result in nasal provocation test or eosinophil count test in nasal fluid, according to the diagnostic classification for allergy described in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2009* or *Practical Guideline for the Management of Allergic Rhinitis in Japan 2013*

<sup>9</sup> After placebo was administered orally twice daily in a single-blind manner in the 1 week run-in period (696 subjects), subjects were randomized if their averages of the paroxysmal sneezing score and nasal discharge score were both  $\geq 2$  (average scores were calculated in the same manner as in Study TAU-284-17).

<sup>10</sup> The total score obtained according to the severity criteria described in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2013* by summing each score of paroxysmal sneezing, nasal discharge, and nasal congestion, ranging from 0 to 4 points, based on the nasal allergy diary journalized by each subject's guardian. The averages of the total score and individual nasal symptom scores were obtained using only data on a day when all scores of the 3 major nasal symptoms were available. When the investigator (or sub-investigator) assessed that there was an event with an impact on the nasal symptom evaluation, data on that day were excluded.

Adverse drug reactions were reported by 4 of 240 subjects (1.7%) in the Talion 20 mg/day group and 6 of 232 subjects (2.6%) in the placebo group.

**3.(ii).A.(3) Japanese phase III study in pediatric patients with atopic dermatitis (5.3.5.1-3, Study TAU-284-19 [March to November 2013])**

A ketotifen fumarate (KTF)-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of Talion in pediatric patients aged  $\geq 7$  and  $\leq 15$  years with atopic dermatitis<sup>11</sup> (target sample size of 300 [150 per group]).

Talion 10 mg or KTF dry syrup (1 mg as ketotifen) was to be administered orally twice daily after breakfast and at bedtime for 2 weeks using the double-dummy technique. From enrollment to the end of the study period, 0.1% hydrocortisone ointment (Locoid Ointment) was to be topically applied to the dermatitis sites excluding the face, head, and neck, and the number of applications per day and the application amount per area of rash were to be generally the same for all subjects throughout the study period.

All of the 303 randomized<sup>12</sup> subjects (151 in the Talion group, 152 in the KTF group) were included in the FAS, and the safety and efficacy analysis sets. The study was discontinued in a total of 2 of 151 subjects (1.3%) in the Talion group and 2 of 152 subjects (1.3%) in the KTF group, and the main reasons included investigator's decision (2 of 151 subjects [1.3%] in the Talion group, 1 of 152 subjects [0.7%] in the KTF group).

The primary efficacy endpoint was the change from baseline in the pruritus score<sup>13</sup>, and is shown in Table 6. The upper bound of the 95% confidence interval (CI) of the between-group difference did not exceed the pre-specified non-inferiority margin (0.4), and therefore the non-inferiority of Talion over KTF has been demonstrated.

**Table 6. Change from baseline to final assessment (FAS) in the pruritus score**

	Talion group	KTF group
Baseline <sup>a)</sup>	2.418 ± 0.457 (151)	2.398 ± 0.469 (152)
Final assessment <sup>b)</sup>	1.744 ± 0.749 (151)	1.767 ± 0.738 (151)
Change from baseline	-0.674 ± 0.723 (151)	-0.634 ± 0.762 (151)
Difference from the KTF group [95% CI] <sup>c)</sup>	-0.031 [-0.191, 0.129]	

Mean ± SD (number of subjects)

a) Average of the last 3 days' pruritus score in the run-in period

b) Average of the last 3 days' pruritus score in the treatment period

c) ANCOVA model with the treatment group and the baseline value as explanatory variables

Adverse events were reported by 29 of 151 subjects (19.2%) in the Talion group and 27 of 152 subjects (17.8%) in the KTF group. Adverse events reported by  $\geq 2\%$  of subjects in either group included nasopharyngitis (3 of 151 subjects [2.0%] in the Talion group, 6 of 152 subjects [3.9%] in the KTF group), somnolence (3 of 151 subjects [2.0%] in the Talion group, 6 of 152 subjects [3.9%] in the KTF group), and diarrhoea (3 of 151 subjects [2.0%] in the Talion group, 1 of 152 subjects [0.7%] in the KTF group). There were no deaths or serious adverse events. Adverse events leading to discontinuation included headache/somnolence (1 of 152 subjects [0.7%]) in the KTF group. These events were mild and moderate in severity, respectively, and were assessed as causally related to the study drug, but the outcomes were reported as "recovered/resolved."

Adverse drug reactions were reported by 3 of 151 subjects (2.0%) in the Talion group and 8 of 152 subjects (5.3%) in the KTF group.

<sup>11</sup> Key inclusion criteria at enrollment: Patients with a diagnosis of atopic dermatitis, according to the diagnostic criteria described in the *Guideline for the Management of Atopic Dermatitis 2009*: The Japanese Dermatological Association

<sup>12</sup> After 0.1% hydrocortisone ointment was used in the 1 week run-in period (328 subjects), subjects who met all of the following criteria were randomized: (a) Subjects who completed all entries of the pruritus diary for the last 3 days of the run-in period, (b) subjects who had mild or worse pruritus scores either at daytime or nighttime every day during the last 3 days of the run-in period, and (c) subjects who used 0.1% hydrocortisone ointment on all days during the last 3 days of the run-in period.

<sup>13</sup> Defined as a daytime or nighttime score, whichever is higher, each of which was determined using a scale ranging from 0 to 4 points according to each subject's symptoms based on the pruritus diary journalized by each subject or his/her guardian. (Kawashima, et al. *Japanese Journal of Clinical Dermatology*. 2002;56:692-697)

### 3.(ii).A.(4) Japanese long-term treatment study in pediatric patients with perennial allergic rhinitis (5.3.5.2-1, Study TAU-284-18 [June to November 2013])

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of Talion in pediatric patients aged  $\geq 7$  and  $\leq 15$  years with perennial allergic rhinitis<sup>14</sup> (target sample size of 50).

Talion 10 mg was to be administered orally twice daily after morning and evening meals (or at bedtime) for 12 weeks.

All of the 58 treated subjects<sup>15</sup> were included in the FAS and the safety and efficacy analysis sets. The study was discontinued in a total of 2 of 58 subjects (3.4%), and the reasons included consent withdrawal (1 subject) and investigator's decision (1 subject).

Adverse events were reported by 37 of 58 subjects (63.8%), and the major events are shown in Table 7. There were no deaths, serious adverse events, or adverse events leading to discontinuation.

Adverse drug reactions were reported by 2 of 58 subjects (3.4%).

**Table 7. Adverse events reported by  $\geq 2\%$  of subjects (safety analysis set, n = 58)**

Nasopharyngitis	19 (32.8)
Upper respiratory tract inflammation	5 (8.6)
Otitis externa	3 (5.2)
Pharyngitis	3 (5.2)
Epistaxis	2 (3.4)
Eczema	2 (3.4)
Liver function test abnormal	2 (3.4)

Number of subjects (%)

The efficacy endpoint is the change from baseline (mean  $\pm$  SD) in the total score of 3 major nasal symptoms<sup>16</sup> (paroxysmal sneezing, nasal discharge, nasal congestion, which was  $-0.943 \pm 1.549$  (57 subjects),  $-1.388 \pm 1.465$  (56 subjects),  $-1.433 \pm 1.880$  (56 subjects), and  $-1.451 \pm 1.707$  (56 subjects) at 2, 4, 8, and 12 weeks post-dose, respectively.

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

#### 3.(ii).B.(1) Efficacy

##### (a) Efficacy against allergic rhinitis

The applicant's explanation for the failure to demonstrate the superiority of Talion over placebo in Study TAU-284-17, and the design of Study TAU-284-20, an additionally conducted confirmatory study:

A post-hoc exploratory subgroup analysis was performed on the change from baseline to final assessment in the total score of 3 major nasal symptoms in Study TAU-284-17 according to the baseline total score. The results showed that there was no substantial difference between the Talion 20 mg/day or 10 mg/day group and the placebo group in subjects with relatively mild baseline nasal symptoms with a total score of  $< 6$ , as shown in Table 8. However, in subjects with a total score of  $\geq 6$ , the difference between the Talion 20 mg/day and placebo groups (20 mg/day group - placebo group) was  $-0.54$ , indicating a trend toward a greater improvement in the 20 mg/day group than in the placebo group. The difference between the Talion 10 mg/day and placebo groups (10 mg/day group - placebo group) was  $-0.11$ , indicating no substantial difference.

<sup>14</sup> Key inclusion criteria: Patients with (a) a positive result in skin testing (intracutaneous or scratch testing) or in serum specific IgE antibody quantitation for house dusts or mites; (b) a positive result in nasal provocation test or eosinophil count test in nasal fluid; and (c) the average total score of 3 major nasal symptoms of  $\geq 3$  during the run-in period, according to the diagnostic classification for allergy described in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2009* or *Practical Guideline for the Management of Allergic Rhinitis in Japan 2013*

<sup>15</sup> Treatment duration:  $\leq 14$  days in 1 subject (1.7%);  $> 28$  and  $< 42$  days in 1 subject (1.7%); and  $> 70$  days in 56 subjects (96.6%) Compliance:  $> 80\%$  in 58 subjects (100%)

<sup>16</sup> The total score obtained according to the severity criteria described in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2013* by summing each score of paroxysmal sneezing, nasal discharge, and nasal congestion, ranging from 0 to 4 points, based on the nasal allergy diary journalized by each subject's guardian.

**Table 8. Difference from the placebo group in the change from baseline in the total score of 3 major nasal symptoms in Study TAU-284-17 by the baseline total score<sup>a)</sup>**

Baseline		Talion 10 mg/day		Talion 20 mg/day	
		No. of subjects Talion group /placebo group	Total score [95% CI]	No. of subjects Talion group /placebo group	Total score [95% CI]
Total score	≥4 and <6	88/81	-0.18 [-0.64, 0.29]	85/81	0.11 [-0.36, 0.58]
	≥6	73/81	-0.11 [-0.63, 0.40]	81/81	-0.54 [-1.04, -0.04]

a) ANCOVA model with the treatment group and the baseline value as explanatory variables

Furthermore, a post-hoc exploratory subgroup analysis was performed in order to evaluate the effect of baseline individual nasal symptom scores (paroxysmal sneezing, nasal discharge, nasal congestion scores) on the change from baseline to final assessment in the total score of 3 major nasal symptoms or in individual nasal symptom scores. The results in table 9 showed that, in the subgroup of subjects with a baseline score of paroxysmal sneezing of 2 or 3, as compared with the subgroup of subjects with a baseline score of paroxysmal sneezing of ≤1, improvement tended to be substantially greater in the Talion 20 mg/day group than in the placebo group in the change from baseline to final assessment in both the total score of 3 major nasal symptoms and in each score of individual symptoms. No same trend was observed for the difference between the Talion 10 mg/day and placebo groups.

Based on the results of these post-hoc exploratory analyses, the failure to demonstrate the superiority of Talion over placebo in Study TAU-284-17 may be attributable to failure to precisely detect the change in symptoms (especially in subjects with mild symptoms) due to the generally greater difficulty identifying symptoms in children than in adults.

In addition, standardization of the evaluation procedure may not have been adequate because some subjects reported unexpectedly large numbers of paroxysmal sneezing episodes and nose blowing in Study TAU-284-17.

**Table 9. Difference from the placebo group in the changes from baseline in the total and individual scores of 3 major nasal symptoms in Study TAU-284-17 by baseline symptom score**

Baseline		Talion 10 mg/day			Talion 20 mg/day		
		No. of subjects Talion group /placebo group	Total score	Symptom score	No. of subjects Talion group /placebo group	Total score	Symptom score
Paroxysmal sneezing	0	17/13	0.13 ± 1.55	0.07 ± 0.52	24/13	-0.09 ± 1.61	0.16 ± 0.61
	1	81/77	-0.31 ± 1.49	0.00 ± 0.70	77/77	-0.09 ± 1.53	0.06 ± 0.75
	2-3	63/72	-0.03 ± 1.64	0.05 ± 0.83	65/72	-0.40 ± 1.73	-0.13 ± 0.88
Nasal discharge	0						
	1						
	2-3	161/161	-0.13 ± 1.57	-0.06 ± 0.80	166/161	-0.19 ± 1.65	-0.11 ± 0.77
Nasal congestion	0	6/5	0.03 ± 1.55	-0.03 ± 0.43	3/5	1.53 ± 1.80	0.13 ± 0.49
	1	70/74	-0.24 ± 1.64	0.06 ± 0.68	79/74	-0.15 ± 1.65	-0.01 ± 0.64
	2-3	85/83	-0.03 ± 1.51	-0.01 ± 0.74	84/83	-0.31 ± 1.63	-0.05 ± 0.76

Mean ± SD

Based on the above, the design of Study TAU-284-17 was modified, by incorporating the following changes, into the design of Study TAU-284-20.

- In Study TAU-284-17, key inclusion criteria included the following: subjects must have an average nasal discharge score of ≥2 and a total score of 3 major nasal symptoms of ≥4, during the run-in period. However, the above post-hoc analysis suggested that precise detection of the change in symptoms may be possible among subjects with both scores of paroxysmal sneezing and nasal discharge at baseline of ≥2. Moreover, second-generation antihistamines are classified as therapeutic drugs for sneezing/rhinorrhea type allergies in the *Practical Guideline for the Management of Allergic Rhinitis in Japan 2009*. Taking account of the above, the following should be included in

the key inclusion criteria of Study TAU-284-20: subjects must have the average paroxysmal sneezing score of  $\geq 2$  and a nasal discharge score of  $\geq 2$  during the run-in period.

- In order to standardize the evaluation procedure for nasal symptoms, the evaluation training procedure was revised. Also, an electronic patient diary system was adopted in order to prevent subjects from journalizing multiple days' nasal allergy diary at one time and to identify the subjects' nasal symptoms at the right time.
- According to the 4-level scale used in Study TAU-284-17 to derive the nasal symptom score, subjects with a daily average number of paroxysmal sneezing episodes or nose blowing of 1 to 5, 6 to 10, and  $\geq 11$  were to receive 1, 2, and 3 points, respectively. Therefore, patients who had paroxysmal sneezing episodes or blew their nose frequently may not have been identified as those achieving lower scores even though their number of paroxysmal sneezing episodes or frequency of nose blowing decreased after study drug administration. Thus, in Study TAU-284-20, the scale to derive nasal symptom score was modified to a 5-level scale, incorporating a level applied to subjects with a daily average number of paroxysmal sneezing episodes or nose blowing of  $\geq 21$ .

Plasma concentrations of unchanged bepotastine in children aged 7 to 15 years who received 10 mg/dose of Talion, the dose approved for adults, were generally similar to those in adults receiving the same dose, and although the exposure may be higher in children around 7 years of age than in adults, the difference was not considered relevant to safety problems [see "3.(i) Summary of biopharmaceutic studies and clinical pharmacology studies"]. In addition, the above post-hoc analysis indicated no efficacy of Talion at 10 mg/day (5 mg/dose, twice daily). Thus, only 20 mg/day (10 mg/dose, twice daily) was selected as the dosage to be studied in Study TAU-284-20.

Because the efficacy of Talion 20 mg/day has been demonstrated in Study TAU-284-20, which was conducted additionally in light of the above considerations, the efficacy of Talion 10 mg twice daily in pediatric patients aged  $\geq 7$  years with allergic rhinitis has been demonstrated.

PMDA's view:

Although the confirmatory study (Study TAU-284-17) conducted in pediatric patients with perennial allergic rhinitis failed to demonstrate the efficacy of Talion, the applicant's discussion on its cause and measures taken for the additional confirmatory study (Study TAU-284-20) were reasonable to a certain extent. Also, as shown in Table 10, the results from the post-hoc exploratory analysis in subjects who participated in Study TAU-284-17 with both baseline paroxysmal sneezing and nasal discharge scores of  $\geq 2$  were generally consistent with the results from Study TAU-284-20. Taking account of the above, it is possible to consider that the efficacy of Talion 10 mg twice daily in pediatric patients aged  $\geq 7$  years with allergic rhinitis has been demonstrated based on the data from Study TAU-284-20.

**Table 10. Changes from baseline in the total score of 3 major nasal symptom in pediatric patients with allergic rhinitis with both baseline paroxysmal sneezing and nasal discharge scores of  $\geq 2$  in Studies TAU-284-17 and TAU-284-20<sup>a)</sup>**

	Study TAU-284-17		Study TAU-284-20	
	Talion 20 mg/day	Placebo	Talion 20 mg/day	Placebo
Change	-1.4 $\pm$ 1.7 (65)	-1.0 $\pm$ 1.7 (71)	-1.5 $\pm$ 1.4 (239)	-1.1 $\pm$ 1.5 (232)
Difference from the placebo group <sup>b)</sup> [95% CI]	-0.42 $\pm$ 0.29 [-0.98, 0.15]	/	-0.40 $\pm$ 0.13 [-0.66, -0.15]	/

a) Obtained by using the 4-level scale used in Study TAU-284-17

b) ANCOVA model using the treatment group and the baseline value as explanatory variables

**(b) Efficacy against skin disorders**

Because topical steroids may be effective for pruritus, PMDA asked the applicant to explain the possible effect of the concomitant use of 0.1% hydrocortisone ointment (topical steroid), which was allowed throughout the study period, on the efficacy evaluation in Study TAU-284-19.

The applicant's explanation:

In Study TAU-284-19, 0.1% hydrocortisone ointment was only allowed as topical steroid, the standard dose of which was 1 finger-tip unit per rash area equivalent to two adult palms, and the number of applications per day and the application amount per rash area was specified to be identical for all subjects in order to limit variability in dosage as much as possible. Subjects who had symptoms of mild or worse after receiving 0.1% hydrocortisone ointment during the run-in period were to be randomized. The daily dose<sup>17</sup> of concomitant 0.1% hydrocortisone ointment before the start of study treatment was  $1.46 \pm 0.61$  in the Talion group and  $1.46 \pm 0.64$  in the KTF group, and that at the final assessment was  $1.34 \pm 0.56$  in the Talion group and  $1.38 \pm 0.62$  in the KTF group; thus, no substantial difference was observed between the two groups. Furthermore, there was no substantial difference between the two groups in the mean of change in the pruritus score by baseline daily dose of 0.1% hydrocortisone ointment or by dose modification during study treatment, as shown in Table 11.

Based on the above, concomitant use with 0.1% hydrocortisone ointment is unlikely to have affected the efficacy evaluation of Talion.

**Table 11. Change in the pruritus score from baseline to final assessment by daily dose of 0.1% hydrocortisone ointment before the start of study treatment or by dose modification during study treatment**

		Talion	KTF
Daily dose before the start of study treatment	$\geq 1.0$ and $< 2.0$	$-0.560 \pm 0.683$ (97)	$-0.531 \pm 0.628$ (98)
	$\geq 2.0$ and $< 3.0$	$-0.858 \pm 0.752$ (49)	$-0.789 \pm 0.917$ (49)
	$\geq 3.0$ and $< 4.0$	$-0.553 \pm 0.387$ (3)	-1.000 (1)
	$\geq 4.0$ and $\leq 5.0$	$-1.835 \pm 0.714$ (2)	$-1.333 \pm 1.528$ (3)
Dose modification during study treatment <sup>a)</sup>	Increased	$-0.385 \pm 0.489$ (13)	$-0.334 \pm 0.534$ (8)
	Not changed	$-0.654 \pm 0.724$ (104)	$-0.575 \pm 0.697$ (117)
	Reduced	$-0.843 \pm 0.766$ (34)	$-0.987 \pm 0.985$ (26)

Mean  $\pm$  SD (number of subjects)

a) "Escalated," "not changed," and "reduced" were defined as the type of dose modification in subjects for whom the steroid score (averaged, see footnote) during the last 3 days of the treatment period was higher than, equal to, and lower than that during the last 3 days of the run-in period, respectively.

PMDA's view:

PMDA accepted the applicant's response and concluded that the efficacy of Talion at 10 mg twice daily in pediatric patients aged  $\geq 7$  years with atopic dermatitis has been demonstrated based on the submitted study data.

### 3.(ii).B.(2) Safety

The applicant's explanation on the safety of Talion in children based on the pooled safety data from the Japanese phase III studies (Studies TAU-284-17, TAU-284-19, and TAU-284-20) and from the Japanese long-term treatment study (Study TAU-284-18) in pediatric patients aged 7 to 15 years with perennial rhinitis allergic or atopic dermatitis:

The incidences of adverse events in the bepotastine 10 mg/day and 20 mg/day groups were 18.6% (30 of 161 subjects) and 21.5% (132 of 615 subjects), respectively, and did not differ substantially from those in the placebo and KTF groups, which were 19.2% (76 of 395 subjects) and 17.8% (27 of 152 subjects), respectively. Adverse events reported by  $\geq 2\%$  of subjects in any one of the groups included nasopharyngitis (8 of 161 subjects [5.0%] in the 10 mg/day group, 32 of 615 subjects [5.2%] in the 20 mg/day group, 6 of 152 subjects [3.9%] in the KTF group, 20 of 395 subjects [5.1%] in the placebo group), pharyngitis (5 of 161 subjects [3.1%] in the 10 mg/day group, 15 of 615 subjects [2.4%] in the 20 mg/day group, 10 of 395 subjects [2.5%] in the placebo group), somnolence (5 of 615 subjects [0.8%] in the 20 mg/day group, 6 of 152 subjects [3.9%] in the KTF group, 1 of 395 subjects [0.3%] in the placebo group), epistaxis (5 of 161 subjects [3.1%] in the 10 mg/day group, 11 of 615 subjects [1.8%] in the 20 mg/day group, 1 of 152 subjects [0.7%] in the KTF group, 2 of 395 subjects [0.5%] in the placebo group).

Adverse events that had not been reported in Japanese clinical studies in adult subjects but were reported only in bepotastine 20 mg/day group in Japanese clinical studies in children included epistaxis (5 of 161 subjects [3.1%] in the 10 mg/day group, 11 of 615 subjects [1.8%] in the 20 mg/day group), otitis externa

<sup>17</sup> Mean  $\pm$  SD of 6-level steroid score (5, 2 tubes; 4, 1.5 to  $< 2$  tubes; 3, 1 to  $< 1.5$  tubes; 2, 0.5 to  $< 1$  tube; 1,  $< 0.5$  tubes; 0, not used)

(4 of 615 subjects [0.7%] in the 20 mg/day group), etc. Adverse events that occurred in the 20 mg/day group in Japanese clinical studies in pediatric subjects at a higher incidence than in Japanese clinical studies in adults included nasopharyngitis (32 of 615 subjects [5.2%]), pharyngitis (15 of 615 subjects [2.4%]), and upper respiratory tract inflammation (6 of 615 subjects [1.0%]). Most of the adverse events reported in children were infections that were considered as accidental events due to seasonal variations.

The incidence of adverse drug reactions in 236 treated children aged <15 years (mean treatment duration, 23.9 days [range, 3-43 days]; mean daily dose, 20 mg/day in 185 of 236 subjects [78.4%] and <20 mg/day in 51 of 236 subjects [21.6%]) collected from the drug use-results survey on rhinitis allergic (survey period, October 2000 to September 2003), urticaria, and pruritus associated with skin disorders (survey period, March 2002 to February 2004) was 1.7% (4 of 236 subjects; somnolence in 3 subjects, glossitis in 1 subject), and did not differ substantially from that in subjects aged ≥15 years (2.0% [85 of 4217 subjects]) collected from the same survey. In addition, the incidence of adverse drug reactions in 1316 treated children with rhinitis allergic aged <15 years (mean treatment duration, 40.1 days [range, 1-327 days]; mean daily dose, 20 mg/day in 960 of 1316 subjects [73.4%] and 10 mg/day in 311 of 1316 subjects [23.8%]) collected from the specified drug use-results survey of children conducted retrospectively (survey period, July 2001 to June 2002) was 1.1% (14 of 1316 subjects), and the major events included somnolence (5 subjects) and thirst and urticaria (2 subjects each). Serious adverse drug reactions were not reported for children in any of these surveys.

PMDA asked the applicant to explain the risk of neuropsychiatric adverse events in children such as somnolence and impaired performance, which may be associated with antihistamines, by comparing the incidences of these events with those in adults in Japanese clinical study data and post-marketing safety information.

The applicant's explanation:

The incidence of neuropsychiatric disorders noted in Japanese clinical studies in pediatric and adult subjects is shown in Table 12. There was no trend toward a higher incidence in children than in adults. The incidence of somnolence was 0.9% (2 of 224 subjects) in children aged <10 years, 0.9% (2 of 229 subjects) in children aged ≥10 and <13 years, and 0.6% (1 of 162 subjects) in children aged ≥13 years, indicating no substantial age difference. Adverse events related to impaired performance were not reported.

Adverse drug reactions of neuropsychiatric disorders reported from the drug use-results surveys and specified drug use-results surveys included somnolence (8 of 1552 subjects [0.5%]) in subjects aged <15 years, and included somnolence (56 of 4217 subjects [1.3%]), dizziness (4 of 4217 subjects [0.1%]), and headache (3 of 4217 subjects [0.1%]) in subjects aged ≥15 years.

Based on the above, the risk of neuropsychiatric adverse events is less likely to be elevated in children than in adults.

**Table 12. Major neuropsychiatric disorders in pediatric and adult subjects reported from Japanese clinical studies**

	Children			Adults			
	Talion 10 mg/day (N = 161)	Talion 20 mg/day (N = 615)	Placebo (N = 395)	Talion 5 mg/day (N = 106)	Talion 10 mg/day (N = 241)	Talion 20 mg/day (N = 917)	Talion 40 mg/day (N = 180)
Neuropsychiatric disorders	2 (1.2)	11 (1.8)	3 (0.8)	8 (7.5)	18 (7.5)	66 (7.2)	19 (10.6)
Headache	2 (1.2)	6 (1.0)	2 (0.5)	4 (3.8)	2 (0.8)	8 (0.9)	2 (1.1)
Somnolence <sup>a)</sup>	0	5 (0.8)	1 (0.3)	4 (3.8)	14 (5.8)	52 (5.7)	17 (9.4)
Heaviness of head	0	0	0	0	0	2 (0.2)	0
Dizziness	0	0	0	0	0	5 (0.5)	0
Light-headedness	0	0	0	0	1 (0.4)	1 (0.1)	0
Shaking hand	0	0	0	0	0	0	1 (0.6)
Numbness in hand	0	0	0	0	0	0	1 (0.6)
Dysgeusia	0	0	0	0	1 (0.4)	1 (0.1)	0
Numbness in backside of tongue	0	0	0	0	1 (0.4)	0	0

Number of subjects (%)

a) "Sleepiness" in the case of adults

PMDA's view:

The submitted clinical study data, etc., suggested no more particular concerns of Talion 10 mg administered twice daily in children aged 7 to 15 years than those in adult subjects. However, given that Talion is used in children of school age, and that a trend toward higher plasma concentrations of unchanged bepotastine in children around 7 years of age compared with adult subjects has been suggested [see "3.(i) Summary of biopharmaceutic studies and clinical pharmacology studies"], the occurrence of neuropsychiatric adverse events including somnolence and impaired performance in children in routine clinical settings should be investigated continuously.

### **3.(ii).B.(3) Indication and dosage and administration**

Based on the review in "3.(ii).B.(1) Efficacy" and "3.(ii).B.(2) Safety," PMDA concluded that the proposed indication of Talion for children, that is, "allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, cutaneous pruritus)," which is the same as that of other drugs in the same class, is acceptable. The proposed dosage and administration, that is, "the usual dosage for children aged  $\geq 7$  years is 10 mg as Talion administered orally twice daily" is also acceptable.

### **3.(ii).B.(4) Post-marketing investigations**

The applicant explained that although a certain amount of information has been collected on the safety of Talion in children via the previously conducted post-marketing surveillance, the specified drug use-results survey for children was retrospective in nature. Thus, the safety and efficacy of Talion in routine clinical settings will be further investigated via additional prospective post-marketing surveillance.

PMDA considers that the occurrence of neuropsychiatric adverse events in children should be continuously investigated via post-marketing surveillance.

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

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

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application. 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 application (5.3.5.1-2, 5.3.5.1-3). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

## **IV. Overall Evaluation**

Based on the submitted data, the efficacy of Talion in children aged  $\geq 7$  years with allergic rhinitis, urticaria, and pruritus associated with skin disorders (eczema/dermatitis, cutaneous pruritus) has been demonstrated and its safety is acceptable in view of its observed benefits. This application is considered of clinical significance because it offers a new option of antiallergic therapy for children. Although no particular problem with the safety of Talion in children aged  $\geq 7$  years has been raised based on the submitted clinical study data etc., the occurrence of neuropsychiatric adverse events in routine clinical settings should be further investigated via post-marketing surveillance.

PMDA considers that this application may be approved if Talion is not considered to have any particular problems based on comments from the Expert Discussion.

## Review Report (2)

April 15, 2015

### I. Product Submitted for Registration

[Brand name]	Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, Talion OD Tablets 10 mg
[Non-proprietary name]	Bepotastine Besilate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	May 30, 2014

### II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. 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 the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

#### (1) Efficacy, indication, and dosage and administration

The conclusion of PMDA on the efficacy, indication, and dosage and administration of "Talion Tablets 5 mg, Talion Tablets 10 mg, Talion OD Tablets 5 mg, and Talion OD Tablets 10 mg" (hereinafter collectively referred to as Talion) as described in the Review Report (1) was supported by the expert advisors.

#### (2) Safety and risk management plan (draft)

The conclusion of PMDA on the safety of Talion as described in the Review Report (1) was supported by the expert advisors. There was a comment from the expert advisors as well that based on the previous reports regarding approved antihistamines, the incidence of neuropsychiatric adverse events associated with Talion should be carefully and continuously investigated via post-marketing surveillance, etc.

Based on the review in "3.(ii).B.(2) Safety" and "3.(ii).B.(4) Post-marketing investigations" of the Review Report (1) and the comments from the expert advisors, PMDA concluded that the risk management plan (draft) should include the safety and efficacy specifications described in Table 13 and that the applicant should conduct additional pharmacovigilance activities shown in Table 14.

**Table 13. Safety and efficacy specifications in the risk management plan (draft)**

Safety specifications		
Important identified risks	Important potential risk	Important missing information
• None	• Somnolence	• None
Efficacy specifications		
• Efficacy in routine clinical settings		

**Table 14. Outline of additional pharmacovigilance activities and risk minimization activities in the proposed risk management plan (draft)**

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified drug use-results survey	• None

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the above issues.

The applicant explained that a specified drug use-results survey with a 12-week observation period and a target sample size of 350 will be conducted in children aged  $\leq 15$  years with rhinitis allergic, urticaria,

