TALION®

bepotastine besilate

Mitsubishi Tanabe Pharma

Summary of Product Characteristic

1. NAME OF THE MEDICINAL PRODUCT

TALION® 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(INN: Bepotastine)

Each tablet contains 10 mg of Bepotastine besilate.

3. PHARMACEUTICAL FORM

Film-coated tablet

A white film-coated tablet with secant line

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

TALION® is indicated for treatment of allergic rhinitis and urticaria.

4.2 Posology and method of administration

Posology

Usually, for adults, 10 mg of bepotastine besilate as a single dose is orally administered twice daily. The dosage may be adjusted depending on the patient's age and symptoms.

Special population

Patients with renal impairment:

The blood concentration of bepotastine may be increased and remain persistently high. This product should be administered with care such as starting from lower dosage (e.g. 5 mg per dose). Appropriate therapeutic measures such as reduction of the dose or suspension of this product should be taken if any abnormal findings are observed (see section 4.4).

Elderly patients:

This product is primarily excreted by the kidneys as intact form. Since elderly patients often have reduced renal function, pay appropriate attention to possible persistence of the elevated blood

concentration.

Pediatric patients:

Usually, for children (≥7 years old), 10 mg of bepotastine besilate as a single dose is orally administered twice daily.

The safety of bepotastine besilate in children under 7 years of age has not been established (little clinical experience).

Method of administration

TALION® is for oral use.

4.3 Contraindication

TALION® is contraindicated in the patients with a history of hypersensitivity to any of the ingredients of this product.

4.4 Special warning and precautions for use

1. This product could possibly cause somnolence in some patients. Whoever aims to be riding, driving, operating machine or working at height with a potential risk to fall from height, should test and ensure, in advance, that this product would not cause him/her somnolence.
2. This product should not be taken concomitantly with alcohol-containing beverages.
3. This product should not be used during the first trimester of pregnancy, during the period of lactation, and in children under 2 years of age.
4. This product should be administered with care in the following patients:

1) Patients with renal impairment

   Since this product undergoes little metabolism and is excreted primarily by the kidney in unchanged form, the blood concentration of bepotastine besilate may be increased and remain persistently high. This product should be administered with care such as starting from a lower dosage (e.g. 5mg per dose). Appropriate therapeutic measures such as reduction of the dose or suspension of this product should be taken if any abnormalities are observed (see the 4th paragraph of section 5.2).

2) Patients receiving long-term steroids therapy

   When this product is administered to reduce the dose of steroids in patients receiving long-term steroids therapy, reduce the dose of steroids gradually while closely observing the patients.

3) Patients with seasonal allergic rhinitis

   When this product is administered to patients with seasonal allergic rhinitis, it is recommended that the treatment is started shortly before the start of the season and continued

until the end of the season.

4) Patients who show ineffective response
   If this product shows no effect, do not administer it for long periods without a specific reason.

4.5 Interaction with other medicinal products and other forms of interactions

Not applicable

4.6 Pregnancy and lactation

1) This product is not recommended to be administered to pregnant women or women who may possibly be pregnant. It should be used only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product during pregnancy has not been established and animal studies have shown transfer of this product to the fetus.] (see the 6th paragraph of section 5.2)
2) Use of this product in lactating woman is not recommended. If administration of this product is judged to be essential, lactation should be discontinued during treatment. [An animal study has shown that this product is excreted in breast milk.] (see the 6th paragraph of section 5.2)

4.7 Effects on ability to drive and use machine

Since this product may induce somnolence, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car (see the 8th paragraph of section 5.1).

4.8 Undesirable effects

< Adult >

Clinical studies (clinical trials): Adverse reactions to this product were reported in 137 (9.5%) of 1,446 patients. The major adverse reactions included somnolence (83 events, 5.7%), thirst (16 events, 1.1%), nausea (12 events, 0.8%), stomachache (7 events, 0.5%), diarrhea (7 events, 0.5%), gastric discomfort (6 events, 0.4%), fatigue (4 events, 0.3%) and vomiting (4 events, 0.3%), etc. Laboratory abnormalities suspected to be related to the product were reported in 64 (5.2%) of 1,225 patients, and the major abnormalities included 25 events of increased ALT (GPT) (2.1% of 1,209 patients), 11 events of urinary occult blood (1.1% of 1,020 patients), 10 events of increased gamma-GTP (0.9% of 1,130 patients) and 8 events of increased AST (GOT) (0.7% of 1,210 patients), etc.

Drug use-results survey (from the time of approval to the end of the reevaluation period):

Adverse reactions were reported in 89 (2.0%) of 4,453 patients. The major adverse reactions included somnolence (59 events, 1.3%).

< Children >

Specified drug use-results survey in pediatric patients: Adverse reactions were reported in 14 (1.1%) of 1,316 pediatric patients (5≤, to <15 years old). The major adverse reactions included somnolence (5 events, 0.4%), thirst (2 events, 0.2%), and urticaria (2 events, 0.2%).

Clinical studies (clinical trials): Adverse reactions were reported in 14 (2.3%) of 615 pediatric patients (7≤, to ≤15 years old) who participated in phase III clinical studies. The major adverse reactions included somnolence (5 events, 0.8%), abnormal liver function test (2 events, 0.3%), and increased AST (GOT) (2 events, 0.3%).

If any adverse reactions are observed, appropriate therapeutic measures such as discontinuation of treatment should be taken.

Incidence / Type	≥0.1% and <5%	<0.1%	Incidence unknown
Haematologic		Increased white blood cell count, decreased white blood cell count, increased eosinophils	
Neuropsychiatric	Somnolence, malaise	Headache, headache dull, dizziness	
Gastrointestinal	Thirst, nausea, stomachache, stomach discomfort, diarrhea	Dry mouth, glossitis, vomiting, abdominal pain	Constipation
Hypersensitivity	Rash	Swelling, urticaria	
Hepatic	Increased AST (GOT), increased ALT (GPT), increased γ-GTP	Increased LDH, increased total bilirubin	
Renal	Urinary occult blood	Protein urine, sugar urinary, urobilinogen urine	Decreased urine output, dysuria, urinary retention
Other		Abnormal menstruation	Oedema, palpitations, dyspnoea, numbness, dysgeusia

4.9 Overdosage

Data not available

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

1. Antagonistic action on histamine H_1 receptor

1) Bepotastine besilate is a highly selective antagonist of histamine H_1 receptor. In vitro receptor binding studies have shown no measurable affinity for 5-HT_2, α_1, α_2 or muscarinic receptors.
2) Orally administered bepotastine besilate inhibited the histamine–induced cutaneous vascular hyperpermeability in rats and guinea pigs. In vitro, bepotastine besilate showed dose-dependent inhibition of histamine-induced contraction of tracheal and ileal smooth muscles isolated from guinea pigs.

2. Inhibitory actions on type I allergic reaction
   1) Orally administered bepotastine besilate inhibited passive cutaneous anaphylaxis (PCA) reaction in rats and guinea pigs, as well as anaphylactic shock and antigen-induced airway constriction in guinea pigs.
   2) Orally administered bepotastine besilate inhibited increase in nasal cavity-resistance in experimental allergic rhinitis model guinea pigs and antigen-induced vascular hyperpermeability in the nasal mucosa in rats.
3. Effects on eosinophils
   1) Orally administered bepotastine besilate inhibited platelet activating factor (PAF)-induced eosinophil infiltration in rats and guinea pigs, and antigen-induced eosinophil infiltration in mice.
   2) Orally administered bepotastine besilate inhibited antigen-induced peripheral blood eosinophilia in mice.
4. Effects on cytokine production

   In vitro, bepotastine besilate suppressed interleukin-5 production in human peripheral blood mononuclear cells.
5. Other actions
   1) Bepotastine besilate showed little effects on the central nervous system, respiratory or cardiovascular system, gastrointestinal system, autonomic nervous system or smooth muscle, renal function, and metabolic or hematologic parameters in general pharmacology tests in mice, rats, guinea pigs, rabbits, and dogs.
   2) Bepotastine besilate did not induce sleep in mice and cats or arrhythmia in dogs and guinea pigs.
6. Clinical pharmacology

   When healthy adults were administered a 5- or 10-mg oral dose of bepotastine besilate, histamine-induced cutaneous wheal and erythema reactions were suppressed dose-dependently and inhibitory activity remained significantly higher than the placebo at 12 hours after administration.
7. Clinical efficacy

<Adults>

1) Allergic rhinitis

In clinical trials in patients with allergic rhinitis including double-blind comparative studies, the final global improvement rate ("moderately improved" or "markedly improved") in subjects who received bepotastine besilate at 10 mg twice a day was 63.6% (126/198).

2) Urticaria

In clinical trials in patients with chronic urticaria (except for the double-blind, placebo-controlled, comparative study), the final global improvement rate ("moderately improved" or "markedly improved") in subjects who received bepotastine besilate at 10 mg twice a day was 76.4% (191/250).

In placebo-controlled, double-blind, comparative studies in patients with chronic urticaria, bepotastine besilate orally administered repeatedly at 10 mg twice a day for 7 days decreased symptom scores for pruritus and rash significantly in comparison to the placebo.

Symptom	Group	Number of subjects	Day before administration		At final dose		Change from baseline		Test (non-restricted LSD test)
			Mean	Standard error	Mean	Standard error	Mean	Standard error	
Pruritus	10 mg×2	55	2.75	0.091	1.13	0.122	-1.62	0.141	p<0.0001
	Placebo	54	2.70	0.086	2.56	0.120	-0.15	0.133	
Rash	10 mg×2	55	2.33	0.064	0.84	0.118	-1.49	0.124	p<0.0001
	Placebo	54	2.30	0.063	1.83	0.114	-0.46	0.111	

3) Pruritus resulting from dermatosis (eczema or dermatitis, prurigo, pruritus cutaneous)

In general clinical studies in patients with eczema or dermatitis, prurigo, and pruritus cutaneous, the final global improvement rate ("moderately improved" or "markedly improved") was 64.7% (119/184) in the entire population. In subpopulations stratified by disease, the overall improvement rate was 63.1% (65/103) in the eczema or dermatitis group, 73.2% (30/41) in the prurigo group, and 60.0% (24/40) in the pruritus cutaneous group.

<Children>

1) Allergic rhinitis

In a double-blind comparative study of bepotastine besilate in children (7≤, to ≤15 years old) with a dosing period of 2 weeks, mean changes from baseline (mean ± SD) in total scores for the three cardinal nasal symptoms (paroxysmal sneeze, nasal discharge, and nasal congestion) at the final evaluation were -1.587 ± 1.332 in the 20-mg treatment group (at 10 mg twice daily) and -1.102 ± 1.462 in the placebo group, respectively. An analysis of covariance with treatment group as a factor and baseline score as a covariant demonstrated the superiority of bepotastine besilate at 20 mg/day to placebo ($P < 0.001$).

In a long-term open-label study of bepotastine besilate in children (7≤, to ≤15 years old)

with a dosing period of 12 weeks, mean changes from baseline (mean ± SD) in total scores for the three cardinal nasal symptoms (paroxysmal sneeze, nasal discharge, and nasal congestion) were −0.943 ± 1.549 at Week 2, −1.388 ± 1.465 at Week 4 and −1.451 ± 1.707 at Week 12 in the 20-mg treatment group (at 10 mg twice daily).

2) Atopic dermatitis

In a double-blind comparative study of bepotastine besilate in children (7≤, to ≤15 years old) with a dosing period of 2 weeks, mean changes from baseline (mean ± SD) in pruritus scores (at the final evaluation) were −0.674 ± 0.723 in the bepotastine besilate group (20 mg/day at 10 mg twice daily) and −0.634 ± 0.762 in the ketotifen fumarate group, respectively. An analysis of covariance with treatment group as a factor and baseline score as a covariant demonstrated the non-inferiority of bepotastine besilate at 20 mg/day to ketotifen fumarate dry syrup (upper limit of 95% confidence interval for between-group difference in adjusted mean changes from baseline in pruritus scores: ≤ 0.4).

8. Somnolence and effect on psychomotor ability

1) In a placebo-controlled double-blind comparative study in patients with chronic urticaria, the incidence of somnolence in the treatment group [20 mg/day] (55 patients) was comparable to that in the placebo group (54 patients).

2) In an integrated analysis of four clinical studies in pediatric patients (7≤, to ≤15 years old), the incidence of somnolence was 0.3% (1/395 patients) in the placebo group and 0.8% (5/615 patients) in the treatment group [20 mg/day].

3) When the effect on psychomotor functions was examined by serial addition testing in healthy male adults, the rate of change in correct answers in the treatment group did not differ significantly from that in the placebo group, indicating no effect on psychomotor functions.

5.2 Pharmacokinetic properties

1. Plasma concentration

<Adults>

The pharmacokinetic parameters of bepotastine after administration of a single oral dose of 2.5 to 40 mg bepotastine besilate to healthy male adults were as follows:

Dosage (mg)	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
2.5	0.8 ± 0.1	22.4 ± 2.1	113.7 ±7.0	3.3 ± 0.3
5	1.2 ± 0.2	46.2 ± 4.0	203.6 ± 6.7	2.5 ± 0.1
10	1.2 ± 0.2	101.3 ± 3.5	438.6 ± 29.1	2.4 ± 0.1
20	1.5 ± 0.3	199.5± 13.1	879.7 ± 60.6	2.3 ± 0.1
40	1.6 ± 0.3	393.6 ± 23.7	1916.4 ± 81.1	2.9 ± 0.2

(Mean ± SE, n=6)

No cumulativeness of bepotastine was observed with repeated oral administration of 20 mg twice a day for 7 days and plasma concentration almost reached a steady state at the second day after the start of administration (C_{max} after final dose = 138.4 ± 9.6 ng/mL, mean ± SE, n = 6). Food intake had little influence on the plasma concentration of bepotastine.

<Children>

Plasma concentrations of bepotastine at 1 to 3 hours and 9 to 11 hours after repeated oral administration of bepotastine besilate at 10 mg twice a day for 2 weeks in pediatric patients (7≤, to ≤15 years old) with perennial allergic rhinitis and with atopic dermatitis were as follows:

	Patients with perennial allergic rhinitis		Patients with atopic dermatitis
	$C_{1–3\ h}$	$C_{9–11\ h}$	$C_{9–11\ h}$
Mean ± SD (n)	92.0 ± 56.1 (62)	8.2 ± 4.0 (43)	8.3 ± 4.1 (106)

(ng/mL)

2. Metabolism and excretion

Little metabolites were observed in the plasma and the urine, and 75% to 90% of the administered dose was excreted in intact form (bepotastine) in the urine within 24 hours after administration.

3. Plasma-protein binding rate

When 10 mg of bepotastine besilate was administered as a single oral dose to healthy male adult, plasma-protein binding rates were 55.9% at one hour and 55.0% at two hours after administration.

4. Plasma concentration in patients with renal impairment

When 5 mg of bepotastine besilate was administered as a single oral dose to patients with renal impairment (6 to 70 mL/min of creatinine clearance), a slight increase in the maximum plasma concentration and an obvious increase in AUC were observed in patients with reduced renal function in comparison with those in patients with normal renal function. When this product was repeatedly administered to patients with renal impairment, the maximum plasma concentration in steady state was predicted to increase by 1.2 to 1.8 times compared with that in patients with normal renal function.

Classification of patients with renal impairment (creatinine clearance)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
Patients with normal renal function (n=5) (>70mL/min)	1.2 ± 0.4	55.1 ± 16.8	2.9 ± 0.5	241.1 ± 50.6
Patients with mild renal impairment (n=5) (51-70 mL/min)	1.0 ± 0.0	61.0 ± 10.8	3.1 ± 0.6	304.0 ± 61.7
Patients with moderate or severe renal impairment (n=6) (6-50 mL/min)	3.3 ± 1.0	66.3 ± 7.7	8.5 ± 3.6	969.1 ± 398.3

(Mean ± S.D.)

5. Plasma concentration in elderly

When 10 mg of bepotastine besilate was repeatedly administered to the elderly patients (61.7

to 126.7 mL/min of creatinine clearance) twice daily for 3 days, the maximum plasma concentration after final administration was 103.8 ± 13.2 ng/mL (mean ± SD, n=10).

6. Distribution

1) Blood-brain barrier penetrability (animal study)

The AUC ratio of bepotastine besilate concentrations in brain and in plasma of male rats 8 hours after the intravenous administration (3 mg/kg) was 0.069.

2) Transfer into the fetus (animal study)

Female rats on the 12th day of pregnancy were orally administered ^{14}C-bepotastine besilate (3 mg/kg) and the radioactivity levels in the fetuses and their dams were measured 30 min and 4 hours later.

The radioactivity level of whole bodies of fetuses was 1/2 to 1/3 of that of plasma in dams 30 min and 4 hours after the administration.

The level of amniotic fluid was 1/9 of that of plasma in dams 30 min after the administration and it was 1/3 4 hours later.

In the rats on the 18th day of pregnancy orally administered ^{14}C-bepotastine besilate (3 mg/kg), the levels of radioactivity of all tissues except brain were the highest 30 min after the administration, and decreased with time.

The levels of all tissues except brain and liver were below detection 24 hours after the administration.

3) Excretion in milk (animal study)

The radioactivity level in the milk reached the C_{max} of 0.40 μg Eq/mL 1 hours after the administration in the lactating rats administered ^{14}C-bepotastine besilate (3 mg/kg) on the 11th day after delivery. After that, it decreased with a $t_{1/2}$ of 2.9 hours (2 to 8 hours) and with a $t_{1/2}$ of 6.0 hours (8 to 24 hours). The level decreased to 1/40 of the C_{max} 24 hours after the administration.

5.3 Preclinical safety data

1. Reproductive and developmental toxicity

1) Effects on fertility and the early stage of pregnancy

Bepotastine besilate was repeatedly administered to male rats (9 weeks before mating and during mating) and female rats (2 weeks before mating, during mating and during the first week of gestation) at oral doses of 8, 40, 200 and 1000 mg/kg/day. As the result, one male died and another male was in a moribund state in the 1000 mg/kg/day group. Mydriasis and staining on the lower abdomen due to urine were observed in the groups receiving 200 mg/kg/day or more. As influences on reproductive function, decline conception rate, decreased number of corpora lutea, and decreased number of implantations were observed

in the parental animals in the 1000 mg/kg/day group. In fetuses, the preimplantation loss rate was significantly increased in the 1000 mg/kg/day group, and the number of live fetuses tended to decrease. The NOAEL for fertility and fetus of the parental animals was determined to be 200 mg/kg/day.

2) Effects during fetal organogenesis

Bepotastine besilate was repeatedly administered to female rats (days 7 to 17 of gestation) at oral doses of 10, 100 and 1000 mg/kg/day. One dam died in the 1000 mg/kg/day group. In addition, mydriasis was observed in the 100 mg/kg/day group and staining on the lower abdomen due to urine was observed in the 1000 mg/kg/day group. However, no effects of bepotastine were observed on the reproductive function of dams, or the development of fetuses and neonates.

Repeated oral administration of bepotastien besilate at 20, 100 and 500 mg/kg/day to female rabbits (gestation days 6 to 18) resulted in red urine and decreased food consumption in dams in the groups receiving 100 mg/kg/day or more. However, no effects of bepotastine were observed on the reproductive function of dams or on the development of fetuses.

The NOAEL for reproductive function in dams and for development in fetuses was determined to be 1000 mg mg/kg/day in rats, and 500 mg/kg/day in rabbits, respectively.

3) Effects during the perinatal and lactation periods

Repeated oral administration of bepotastine besilate at 10, 100 and 1000 mg/kg/day to female rats (gestation day 17 to postpartum day 21) resulted in death, mydriasis, and staining on the lower abdomen due to urine in dams in the 1000 mg/kg/day group, as well as birth and lactation disorders. In neonates, decreased viability, delay in development and differentiation, and partial suppression of functional development was observed in the 1000 mg/kg/day group.

The NOAEL was determined to be 100 mg/kg/day for reproductive function in dams and for development in neonates.

2. Other special toxicities

1) Antigenicity

Bepotastine besilate showed no antigenic activity in any of the tests with guinea pigs and mice, including active systemic anaphylaxis test, homologous or heterologous passive cutaneous anaphylaxis tests, and an enzyme-linked immunosorbent test (ELISA).

2) Genotoxicity

Bepotastine besilate showed no genotoxic activity in a reverse mutation study using *Escherichia coli* and *Salmonella typhimurium*, a chromosomal aberration test using cultured cells, and a micronucleus test in mice.

3) Carcinogenicity

Bepotastine besilate showed no carcinogenicity in a 24-month oral dosing study using rats and mice (mice were discontinued at 21 months because of decreased survival in the control and other groups during the treatment period). Total incidence of hepatocellular tumours was increased in female mice of the 200 mg/kg/day group (oral: dietary for 21 months). This was considered to be a species-specific change due to hepatic drug-metabolizing enzyme induction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, Cellulose, Talc, Hypromellose, Macrogol 6000, D-mannitol

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

42 months

6.4 Special precautions for storage

Store at below 30°C. Avoid exposure to humidity after opening the package.

6.5 Nature and contents of container

The products are packed into polyvinylchloride rigid film / aluminum foil blister sheets of 10 tablets. Three or ten blister sheets are packaged in aluminum pillow pack and then in carton box. Carton contains 30 or 100 tablets.

7. MARKETING AUTHORIZATION HOLDER

Mitsubish Tanabe Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

Manufactured by:

Mitsubishi Tanabe Pharma Factory Ltd.
Yamaguchi, Japan

Bulk packaging by:

Tanabe Seiyaku Yoshiki Factory Co., Ltd.

Gifu, Japan

Released by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT[1]

[1] September 2019