CV. SANIC OFFSET		DIAJUKAN TANGGAL :	NO :
RELASI	**PT MITSUBISHI TANABE PHARMA**	**09 / 02 / 2024**	000
NAMA ITEM	**BROCHURE TALION MTID CM**	HASIL ACC DITERIMA OLEH :	
UK JADI	**42 X 18,5 CM**		CATATAN :
WARNA	**HITAM** ■		**REVISI**
LAIN-LAIN		(.....)	

DEPAN

185,00 mm
15,00 mm
35,00 mm
8,00 mm
420,00 mm

Mitsubishi Tanabe Pharma

Anti-allergy agent with selective antagonism for histamine H_1-receptor

TALION ®
Bepotastine besilate
Film-coated Tablet 10 mg

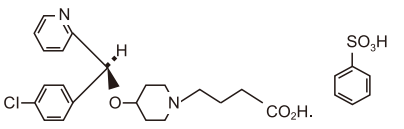
Reg. No. DKL1825202717A1

(COMPOSITION AND DESCRIPTION)

PHYSICOCHEMISTRY

Nonproprietary name : Bepotastine besilate (JAN)
Chemical name : (+)-(S)-4-[4-[(4-Chlorophenyl) (2-pyridyl) methoxy] piperidino] butyric acid monobenzenesulfonate
Molecular formula : $C_{21}H_{25}ClN_2O_3$-$C_6H_6O_3S$: 547.07

Structural formula:



DESCRIPTION:

- Bepotastine besilate occurs as white to pale yellowish white crystals or crystalline powder.
- Bepotastine besilate is very soluble in acetic acid (100), freely soluble in methanol, sparingly soluble in water or ethanol (99.5), slightly soluble in acetonitrile and practically insoluble in diethyl ether.
- The pH of the aqueous solution of bepotastine besilate (1 in 100) is approximately 3.8.
- Melting point: 159 -163 °C
- Partition coefficient: 1.78 (pH 7, octanol/water system)

Brand name	TALION Film-coated Tablet 10 mg
Ingredient/Content (per tablet)	Bepotastine besilate
	10 mg
Inactive Ingredients	Magnesium stearate, Cellulose, Talc, Hydroxypropylmethylcellulose, Macrogol, D-mannitol
Dosage Form	Film-coated Tablets
Color	White
Appearance	(scored)
Size (mm)	Diameter : 7.1 Thickness : 3.0
Weight (g)	0.125
Identification Code	TA 133

(ACTIONS)

PHARMACOLOGY

1. Antagonistic action on histamine H_1 receptor [14-16)]

1) Bepotastine besilate showed selective affinity for H_1 receptor, and showed no affinity for 5-HT_2, alpha$_1$, alpha$_2$ and muscarinic receptors, etc.
2) Oral administration of bepotastine besilate inhibited the histamine–induced enhancement of vascular permeability of skin (in rats and guinea pigs). In vitro study showed that bepotastine besilate dose-dependently inhibited the histamine-induced contraction of isolated guinea pig smooth muscles (bronchus, ileum).

2. Inhibitory actions on type I allergic reaction[15-18)]

1) Oral administration of bepotastine besilate inhibited passive cutaneous anaphylaxis (PCA) reaction (in rats and guinea pigs), anaphylactic shock (in guinea pigs) and antigen-induced bronchoconstriction (in guinea pigs).
2) Oral administration of bepotastine besilate inhibited the increase in nasal cavity-resistance in experimental allergic rhinitis model (guinea pigs) and the enhancement of vascular permeability of nasal mucosa induced by antigen (in rats).

3. Effects on eosinophils[19,20)]

1) Oral administration of bepotastine besilate inhibited platelet activating factor (PAF)-induced eosinophil accumulation (in rats and guinea pigs) and antigen-induced eosinophil infiltration (in mice).
2) Oral administration of bepotastine besilate inhibited peripheral blood eosinophilia (in mice).

4. Effects on cytokine production [21)]

Bepotastine besilate suppressed interleukin-5 production by human peripheral blood mononuclear cells (in vitro).

5. Other actions[14,22,23)]

1) No specific findings with bepotastine besilate have been observed in general pharmacological studies of central nervous system, respiratory/circulatory system, gastrointestinal system, autonomic nervous system/smooth muscle, renal function, metabolic system, and hematological system (in mice, rats, guinea pigs, rabbits and canines).
2) Drowsiness-inducing action (in mice and cats) and arrhythmia-inducing action (in canines and guinea pigs) of bepotastine besilate were not observed.

6. Clinical pharmacology[24)]

In the histamine-induced intradermal reaction test for healthy adult men, oral administration of bepotastine besilate (5 and 10 mg) inhibited dose-dependently wheal and erythema, and the significant inhibited was observed at 12 hours after administration.

PHARMACOKINETICS

1. Plasma concentration [2,3)]

When 2.5 to 40 mg of bepotastine besilate was administered as a single oral dose to healthy adult men, pharmacokinetic parameters of bepotastine are as follows:

Dosage (mg)	Tmax (hr)	Cmax (ng/mL)	AUCo-∞ (ng.hr/mL)	t 1/2 (hr)
2.5	0.8 ± 0.3	22.4 ± 5.1	113.7 ± 17.1	3.3 ± 0.8
5	1.2 ± 0.4	46.2 ± 9.7	203.6 ± 16.4	2.5 ± 0.3
10	1.2 ± 0.4	101.3 ± 8.5	438.6 ± 71.2	2.4 ± 0.2
20	1.5 ± 0.8	199.5±32.2	879.7 ± 148.5	2.3 ± 0.2
40	1.6 ± 0.7	393.6 ± 58.1	1916.4 ± 198.7	2.9 ± 0.6

(mean±S.D., n=6)

No cumulativeness of bepotastine was observed with repeated administration (20 mg, twice daily) for seven days and plasma concentration reached a steady state at the second day after administration (Cmax in final administration=138.4±23.4 ng/mL, mean±S.D., n=6). Food intake had little influence on the plasma concentration of bepotastine.

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 adult men, 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 dysfunction [4)]

When 5 mg of bepotastine besilate was administered as a single oral dose to patients with renal dysfunction (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 drug was repeatedly administered to patients with renal dysfunction, 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 dysfunction (creatinine clearance)	T max (Hour)	Cmax (ng/mL)	T½ (hour)	AUC $_{0-\infty}$ (ng.hr/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 dysfunction (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 dysfunction (n=6) (6-50 mL/min)	3.3 ± 1.0	66.3 ± 7.7	8.5 ± 3.6	969.1 ± 398.3

5. Plasma concentration in elderly [5)]

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 three days maximum plasma concentration after final administration was 103.8 ± 13.2 ng/mL (mean ± SD , n=10).

(CLINICAL STUDIES)

1. Allergic rhinitis[6-8)]

The final global improvement rating (moderately improved or better) of TALION Film-coated Tablets in patients with allergic rhinitis was 63.6 % (126/198) in clinical studies including the double blind comparative study.

2. Urticaria[9-12)]

The final global improvement rating (moderately improved or better) of TALION Film-coated Tablets in patients with chronic urticaria was 76.4 % (191/250) in clinical studies excluding the double blind comparative study with inactive placebo. In the double blind comparative study with inactive placebo in patients with chronic urticaria, this drug significantly reduced the symptom scores of itching level and eruption compared with those of inactive placebo.

DISETUJUI OLEH BPOM : 29/05/2024

ID : EREG100028VR12400023

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Symptom	Drugs	Cases	The day before administration	
			Mean	SE
Itching level	10 mg x 2	55	2.75	0.091
	Inactive placebo	54	2.10	0.086
Eruption	10 mg x 2	55	2.33	0.064
	Inactive placebo	54	2.30	0.063

At final administration		Change in score		Test (infinite LSD method)
Mean	SE	Mean	SE	
1.13	0.122	-1.62	0.141	$p < 0.0001$
2.56	0.120	-0.15	0.133	
0.84	0.118	-1.49	0.124	$p < 0.0001$
1.83	0.114	-0.46	0.111	

INDICATIONS

- Allergic rhinitis
- Urticaria

CONTRAINDICATIONS

(TALION Film-coated Tablets is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any of the ingredients of this product.

DOSAGE AND ADMINISTRATION

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.

PRECAUTIONS

1. **Careful Administration (TALION Film-coated Tablets should be administered with care in the following patients.)**
   Patients with renal dysfunction [The blood concentration of bepotastine may be increased. Since there is a possibility of the persistently elevated blood concentration, this drug should be administered carefully by starting at a low dose (e.g., 5 mg per time). If any abnormal findings are observed, appropriate measures such as reducing the dose or discontinuing this drug should be taken.]

2. **Important Precautions**
   1) Since this drug may induce drowsiness, patients should be cautioned in operating potentially hazardous machinery requiring alertness, such as driving a car.
   2) In cases where patients undergoing long-term steroid therapy require a reduction of the steroid dose due to the use of this drug, the reduction should be implemented gradually under adequate management.
   3) When this drug is administered to patients with seasonal allergic rhinitis, the treatment should be initiated before the start of the high frequency season and continued until the end of season.
   4) If the efficacy of this drug is not observed, it should not be administered on a long-term basis.

3. **Adverse Reaction**
   Clinical studies (trials): Adverse reactions to this drug were reported in 137 (9.5%) of 1,446 patients treated. The major adverse reactions were drowsiness in 83 (5.7%), thirst in 16 (1.1%), nausea in 12 (0.8%), stomachache in 7 (0.5%), diarrhea in 7 (0.5%), gastric discomfort in 6 (0.4%), fatigue in 4 (0.3%) and vomiting in 4 (0.3%), etc. Possible correlations between the drug and abnormal change in clinical laboratory findings were reported in 64 (5.2%) of 1,225 patients treated. The major abnormal changes in clinical laboratory findings were increased ALT (GPT) in 25 (2.1%) of 1,209 patients treated, urinary occult blood in 11 (1.1%) of 1,020, increased gamma-GTP in 10 (0.9%) of 1,130 and increased AST (GOT) in 8 (0.7%) of 1,210, etc.
   Post marketing surveillance (at the fourth safety periodical report): Adverse reactions to this drug were reported in 29 (1.7%) of 1,721 patients treated. The major adverse reactions were drowsiness in 15 (0.9%), etc.
   Special surveillance for child patients[1] : Adverse reactions to this drug were reported in 14 (1.1%) of 1316 child patients treated (between 5 and 15 years of age). The major adverse reactions were drowsiness in 5 (0.4%), thirst in 2 (0.2%) and urticaria in 2 (0.2%), etc.
   If such symptoms are observed, appropriate measures such as discontinuing this drug should be taken.

	5% > ≥0.1%	<0.1%	Incidence unknown
Hematologic	Leukocytosis, Leukopenia, eosinophilia		
Psychoneurologic	Drowsiness, malaise, headache, dizziness	Heavy-headed feeling	
Gastrointestinal	Thirst, nausea, vomiting, stomachache, gastric discomfort, diarrhea	Dry mouth, glossitis, abdominal pain	
Hypersensitivity	Rash	Swelling	
Hepatic	Increased AST (GOT), increased ALT (GPT), increased gamma-GTP, increased LDH, increased total bilirubin		
Renal	Urinary occult blood	Proteinuria, glycosuria, urinary urobilinogen	Decreased urine volume

4. **Use in the Elderly**
   This drug is primarily excreted from the kidneys as intact form. However, since elderly patients often have educed physiological function, pay appropriate attention to possible persistence of the elevated blood concentration.

5. **Use during Pregnancy, Delivery or Lactation**
   1) It is advisable to avoid using this drug in pregnant women or in women who may possible be pregnant. If use of this drug is judged to be essential, it should be administered only when the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this drug in pregnant women has not been established and maternal-fetal transfer of bepotastine into the fetus has been observed in an animal study (in rats).]
   2) It is advisable to avoid using this drug in lactating mothers. If use of this drug is judged to be essential, breast feeding should be discontinued during treatment. [An animal study (in rats) has shown that this drug is excreted in breast milk.]

6. **Pediatric Use**[1]
   The safety of this drug in low birth weight infants, neo-nates, nursing infants, infants or children has not been established (a limited number of clinical experiences available).

7. **Precaution concerning Use**
   Precaution in dispensing:
   For drugs that are dispensed in a press-through package (PTP), the patients should be instructed to remove the drug from the package before use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

HANDLING

Cautions : Use only pursuant to the prescription or direction of a physician, etc.

STORAGE

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

Expiration date : Indicated on package and container

PACKAGING

TALION Film-coated Tablets l0mg : 30 film-coated tablets (10 film-coated tablets x 3) in PTP

ON DOCTOR'S PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

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