SUMMARY OF PRODUCT CHARACTERISTICS

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1. Name of drug product

OLOTEN PLUS EYE DROPS

2. Qualitative and quantitative compositions

One mL of solution contains 2.22 mg olopatadine hydrochloride (2mg as olopatadine)

3. Pharmaceutical Form

Colorless or almost white clear ophthalmic solution in an opaque container

4. Clinical particulars

4.1 Therapeutic indications

Treatment of ocular signs and symptoms of seasonal allergic conjunctivitis

4.2 Posology and method of administration

The recommended therapy is one drop of Oloten Plus Eye Drops in the affected eye(s) one daily.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warning and precautions for use

Oloten Plus Eye Drops is an antiallergic/antihistaminic agent and, although administered topically, is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this treatment.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since Oloten Plus Eye Drops contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

Contact lenses

Patients should be instructed to wait 10-15 minutes after instillation of Oloten Plus Eye Drops before inserting contact lenses. Oloten Plus Eye Drops should not be administered while wearing contact lenses.

4.5 Use in pregnancy and lactation

1) Olopatadine was not teratogenic in rats and rabbits at oral doses of 600 mg/kg and 400 mg/kg, respectively (93,750 times and 62,500 times the maximum recommended ocular human use level, respectively). Given that animal studies are not always predictive of human responses, and that no adequate and well controlled studies in pregnant women have been performed, it should be carefully considered whether the potential benefit to the mother justifies the potential risk to the embryo or foetus.

2) Olopatadine has been identified in the milk of nursing rats following oral administration.

It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk. This preparation should be used with caution in breastfeeding woman.

4.6 Effects on ability to drive and operate machine

As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

4.7 Undesirable effects

Symptoms like Cold or pharyngitis have been reported at an incidence of 10%. The following adverse experiences have been reported in less than 5% of patients:

Ocular symptoms : blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, eye congestion, hypersensitivity, keratitis, lid edema, eye pain, pruritis

Non-ocular symptoms : Asthenia, back pain, cold syndrome, headache, frequent cough, infection, nausea rhinitis, sinusitis and taste perversion.

4.8 Overdoses

No data are available in humans regarding overdose by accidental or deliberate ingestion. Olopatadine has a low order of acute toxicity in animals. Accidental ingestion of the entire contents of a bottle of Oloten Plus Eye Drops would deliver a maximum systemic exposure

of 5 mg olopatadine. This exposure would result in a final dose of 0.5 mg/kg in a 10 kg infant, assuming 100% absorption.

Prolongation of the QTc interval in dogs was observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. A 5 mg oral dose was administered twice-daily for 2.5 days to 102 young and elderly male and female healthy volunteers with no significant prolongation of QTc interval compared to placebo. The range of peak steady-state olopatadine plasma concentrations (35 to 127 ng/ml) seen in this study represents at least a 70-fold safety margin for topical olopatadine with respect to effects on cardiac repolarisation.

In the case of overdose, appropriate monitoring and management of the patient should be implemented.

5. Pharmacological properties

5.1 Pharmacokinetic properties

Olopatadine is absorbed systemically, as are other topically administered medicinal products. However, systemic absorption of topically applied olopatadine is minimal with plasma concentrations ranging from below the assay quantitation limit (<0.5 ng/ml) up to 1.3 ng/ml. These concentrations are 50-to 200-fold lower than those following well tolerated oral doses. From oral pharmacokinetic studies, the half-life of olopatadine in plasma was approximately eight to 12 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as active substance. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

Since olopatadine is excreted in urine primarily as unchanged active substance, impairment of renal function alters the pharmacokinetics of olopatadine with peak plasma concentrations 2.3-fold greater in patients with severe renal impairment (mean creatinine clearance of 13.0 ml/min) compared to healthy adults. Following a 10 mg oral dose in patients undergoing haemodialysis (with no urinary output), plasma olopatadine concentrations were significantly lower on the haemodialysis day than on the non-haemodialysis day suggesting olopatadine can be removed by haemodialysis.

Studies comparing the pharmacokinetics of 10 mg oral doses of olopatadine in young (mean

age 21 years) and elderly (mean age 74 years) showed no significant differences in the plasma concentrations (AUC), protein binding or urinary excretion of unchanged parent drug and metabolites.

A renal impairment study after oral dosing of olopatadine has been performed in patients with severe renal impairment. The results indicate that a somewhat higher plasma concentration can be expected with Oloten Plus Eye Drops in this population. Since plasma concentrations following topical ocular dosing of olopatadine are 50-to 200-fold lower than after well-tolerated oral doses, dose adjustment is not expected to be necessary in the elderly or in the renally impaired population. Liver metabolism is a minor route of elimination. Dose adjustment is not expected to be necessary with hepatic impairment.

5.2 Pharmaco-dynamic properties

Pharmacotherapeutic Group: ophthalmologicals; decongestant and antiallergics; other antiallergics.

ATC code: S01GX 09

Olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of action. It antagonises histamine (the primary mediator of allergic response in humans) and prevents histamine induced inflammatory cytokine production by human conjunctival epithelial cells. Data from *in vitro* studies suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. In patients with patent nasolacrimal ducts, topical ocular administration of Oloten Plus Eye Drops was suggested to reduce the nasal signs and symptoms that frequently accompany seasonal allergic conjunctivitis. It does not produce a clinically significant change in pupil diameter.

5.3 Pre-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Benzalkonium Chloride

Polyethylene Glycol 400

Sodium Chloride

Dibasic Sodium Phosphate Hydrate

Disodium Edetate Hydrate

Hydrochloric Acid

Sodium Hydroxide

Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

24 months from manufactured date

6.4 Special precaution for storage

Preserve in a tight container. Store at room temperature between 2 ~ 25℃.

6.5 Nature and contents of container

Oloten Plus Eye drops is contained in a 5 mL translucent low density polyethylene bottles with HDPE/LDPE cap.

7. Marketing authorization holder

SAMCHUNDANG CO., LTD

Address : SamChunDang Pharmaceutical Co., Ltd. 351, Hyoryeong-ro, Seocho-gu, Seoul, Korea

8. Marketing authorization number

Not applicable

9. Date of first authorization / renewal of authorization

Not applicable

10. Date of revision of the text

July 20, 2017