SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

Ketotifen iPharma (0,25 mg/mL, eye drops, solution)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 0,345 mg ketotifen hydrogen fumarate equivalent to 0,25 mg ketotifen.

Each drop contains approximately 9,3 microgram ketotifen hydrogen fumarate equivalent to 6,7 microgram ketotifen.

Excipient(s) with known effect:

Ketotifen iPharma contains 0,5 mg benzalkonium chloride in each 5 ml bottle which is equivalent to 0,1 mg/mL (0,01 % w/v).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the temporary prevention of itching of the eye due to seasonal allergic conjunctivitis. Safety and efficacy beyond four weeks have not been established.

4.2 Posology and method of administration

Posology

Adults and children (age 3 years and older): Instil 1 drop into the lower conjunctival sac of the eyes, two to three times daily.

Paediatric population

The safety and efficacy of Ketotifen iPharma in children aged from birth to 3 years have not yet been established.

Method of administration

See “Posology”.

The contents and dispenser remain sterile until the original closure is broken.

To avoid contamination do not touch any surface with the dropper tip.

4.3 Contraindications

- Hypersensitivity to ketotifen or to any of the excipients in Ketotifen iPharma listed in section 6.1.
- The safety of administration in pregnancy has not yet been established.
- Contact lenses.

4.4 Special warnings and precautions for use

Use only for ocular instillation.

The possibility of corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations such as Ketotifen iPharma, cannot be excluded, therefore regular ophthalmological examinations are required.

Caution should be exercised in the use of benzalkonium chloride preserved topical medication, such as Ketotifen iPharma, over an extended period in patients with extensive ocular surface disease.

Ketotifen iPharma contains benzalkonium chloride as preservative, which may be absorbed by soft contact lenses and may change the colour of the contact lenses. Ketotifen iPharma should, therefore, not be administered while wearing contact lenses. The lenses should be removed prior to instillation of Ketotifen iPharma and only reinserted 15 minutes after administration.

Benzalkonium chloride may also cause eye irritation, especially with dry eyes or disorders of the cornea.

4.5 Interaction with other medicines and other forms of interaction

If Ketotifen iPharma is used concomitantly with other eye medications, there must be an interval of at least 5 minutes between the two medications to avoid the washing out of the medicine.

The use of ketotifen may potentiate the effect of central nervous system (CNS) depressants, antihistamines and alcohol. Although this has not been observed with Ketotifen iPharma eye drops, the possibility of such effects cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of ketotifen eye drops in pregnant women (see section 4.3). Animal studies using maternally toxic oral doses showed increased pre- and postnatal mortality, but no teratogenicity. Systemic levels after ocular administration are much lower than after oral use. Caution should be exercised when prescribing Ketotifen iPharma to pregnant women.

Breast Feeding

Although animal data following oral administration show excretion into breast milk, topical administration of ketotifen hydrogen fumarate in humans are unlikely to produce detectable quantities in breast milk. The safety of Ketotifen iPharma eye drops during lactation has not been established, therefore not recommended for use during breast feeding.

Fertility

There are no data available on the effect of ketotifen hydrogen fumarate on the fertility in humans.

4.7 Effects on ability to drive and use machines

Ketotifen iPharma may cause drowsiness and blurred vision. Patients who experience blurred vision or somnolence should refrain from driving a vehicle or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Frequent side effects reported were flu syndrome, pharyngitis, rhinitis and eye disorders including eye irritation, eye pain, punctate keratitis and punctate corneal epithelial erosion.

Tabulated list of adverse reactions:

Immune system disorders	**Less frequent**	**Hypersensitivity**
Nervous system disorders	*Less frequent*	Headache
Eye disorders	*Frequent*	Eye irritation, eye pain, punctate keratitis, punctate corneal epithelial erosion
	Less frequent	Vision blurred (during instillation), dry eyes, eyelid disorder, conjunctivitis, photophobia, conjunctival haemorrhage, lacrimation disorder, discharge, mydriasis, burning or stinging, itching.
Respiratory, thoracic and mediastinal disorders	*Frequent*	Flu syndrome, pharyngitis, rhinitis
Gastrointestinal disorders	*Less frequent*	Dry mouth
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, eczema, urticarial
General disorders and administrative site conditions	*Less frequent*	Somnolence

Adverse reactions reported from post-marketing experience:

Immune system disorders	*Frequency not known*	Hypersensitivity reactions including local allergic reaction (mostly contact dermatitis, eye swelling, eyelid pruritis and oedema), systemic allergic reactions including facial swelling/oedema (in some cases associated with contact dermatitis) and exacerbation of pre-existing allergic conditions such as asthma and eczema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

If overdosage occurs, treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other antiallergics. ATC code: S01GX08.

Ketotifen is a histamine H_1-receptor antagonist. In addition, ketotifen in vitro inhibits the release of mediators (e.g., histamine, leukotrienes and prostaglandins, and PAF) from cells involved in immediate Type 1 allergic reactions (mast cells, eosinophils; basophils and neutrophils). Ketotifen in vitro also decreases chemotaxis, activation and degranulation of eosinophils. Increased cAMP levels by phosphodiesterase inhibition may contribute to the cell stabilising effect of ketotifen.

5.2 Pharmacokinetic properties

Absorption

After oral administration, the absorption of ketotifen is almost complete. Bioavailability amounts to approximately 50 % owing to a first-pass effect of about 50 % in the liver.

Distribution

Maximal plasma concentrations are reached within 2 to 4 hours. Protein binding is 75 %.

Elimination

Ketotifen is eliminated biphasically, with a short half-life of 3 to 5 hours and a longer one of 21 hours. About 1 % of the substance is excreted unchanged in the urine within 48 hours and 60 to70 % as metabolites. The main metabolite is the practically inactive ketotifen-N-glucuronide.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans which is considered relevant in connection with use of Ketotifen iPharma eye drops 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, Glycerol (E422), Sodium hydroxide (E524), Water for injections

6.2 Incompatibilities

Ketotifen iPharma contains benzalkonium chloride as preservative, which may be absorbed by soft contact lenses and may change the colour of the contact lenses. See section 4.4.

6.3 Shelf life

Unopened bottle: 2 years

After opening: 28 days

6.4 Special precautions for storage

Store at or below 25 °C.

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 ml solution in a white low-density polyethylene (LDPE) bottle with a transparent LDPE dropper and white tamper-evident high-density polyethylene (HDPE) screw cap. Pack size: 1 bottle packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

54/15.4/0176

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2022

10 DATE OF REVISION OF THE TEXT

10 August 2022