IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0013/113/001
Case No: 2037810

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, **Frimley**, **Camberley**, **Surrey, GU16 7SR**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

BENTIFEN 0.25 mg/ml eye drops solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **11/12/2007** until **29/06/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BENTIFEN 0.25 mg/ml, eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 0.345 mg ketotifen fumarate corresponding to 0.25 mg ketotifen.
Each drop contains 8.5 microgram ketotifen fumarate.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution
Clear, colourless to faintly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of seasonal allergic conjunctivitis.

4.2 Posology and method of administration

Adults, elderly and children (age 3 and older): one drop of BENTIFEN into the conjunctival sac twice a day.

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.

4.4 Special warnings and precautions for use

The formulation of BENTIFEN eye drops contains benzalkonium chloride as a preservative, which may be deposited in soft contact lenses; therefore BENTIFEN eye drops should not be instilled while the patient is wearing these lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.

All eye drops preserved with benzalkonium chloride may possibly discolour soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

If BENTIFEN is used concomitantly with other eye medications there must be an interval of at least 5 minutes between the two medications.

The use of oral dosage forms of ketotifen may potentiate the effect of CNS depressants, antihistamines and alcohol. Although this has not been observed with BENTIFEN eye drops, the possibility of such effects cannot be excluded.

4.6 Pregnancy and lactation

There are no adequate data from the use of ketotifen eye drops in pregnant women. 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 to pregnant women.

Although animal data following oral administration show excretion into breast milk, topical administration to human is unlikely to produce detectable quantities in breast milk. BENTIFEN eye drops can be used during lactation.

4.7 Effects on ability to drive and use machines

Any patient who experiences blurred vision or somnolence should not drive or operate machines.

4.8 Undesirable effects

At the recommended dose, the following undesirable effects have been reported:

Eye disorders:
Common effects: Eye irritation, eye pain, punctate keratitis.
Uncommon effects: Vision blurred (during instillation), dry eye, eyelid disorder, conjunctivitis, photophobia, conjunctival haemorrhage.

Nervous system disorders:
Uncommon effects: Headache.

General disorders and administration site conditions:
Uncommon effects: Somnolence.

Skin and subcutaneous tissue disorders:
Uncommon effects: Rash, eczema, urticaria.

Gastrointestinal disorders:
Uncommon effects: Dry mouth.

Immune system disorders:
Uncommon effects: Hypersensitivity.

4.9 Overdose

No case of overdose has been reported.

Oral ingestion of the contents of a 5 ml bottle would be equivalent to 1.25 mg of ketotifen which is 60% of a recommended oral daily dose for a 3 year old child. Clinical results have shown no serious signs or symptoms after oral ingestion of up to 20 mg of ketotifen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other anti-allergics.
ATC code: S01GX08.

Ketotifen is a histamine H_1-receptor antagonist. *In vivo* animal studies and *in vitro* studies suggest the additional activities of mast cell stabilisation and inhibition of infiltration, activation and degranulation of eosinophils.

5.2 Pharmacokinetic properties

In a pharmacokinetic study conducted in 18 healthy volunteers with BENTIFEN eye drops, plasma levels of ketotifen after repeated ocular administration for 14 days were in most cases below the limit of quantitation (20 pg/ml).

After oral administration, ketotifen is eliminated biphasically with an initial half-life of 3 to 5 hours and a terminal half-life of 21 hours. About 1% of the substance is excreted unchanged in the urine within 48 hours and 60 to 70% as metabolites. The main metabolite is the practically inactive ketotifen-N-glucuronide.

5.3 Preclinical safety data

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

In unopened bottle: 2 years.
After opening: 4 weeks.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

The container is a white-coloured LDPE bottle with a transparent LDPE dropper and a white HDPE screw cap with an integrated safety ring. One bottle contains 5 ml of the solution.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 13/113/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2005

Date of last renewal: 30 June 2005

10 DATE OF REVISION OF THE TEXT

October 2006