Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Voltarol Ophtha Multidose 1mg/ml Eye Drops Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac Sodium 1 mg/ml.

Excipient with known effect: benzalkonium chloride (0.05 mg/ml)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops solution. (Eye drops)

A clear, colourless, odourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For pre and post operative prevention of post-surgery aphakic cystoid macular oedema associated with cataract lens extraction and intraocular lens implantation. In inhibition of intraoperative miosis. In post-operative inflammation in cataract surgery and other surgical interventions. In non-infected inflammatory conditions of the anterior segment of the eye. In inflammation following trauma and non-penetrating injuries (in combination with local anti-infective treatment). Control of ocular pain and discomfort associated with corneal epithelial defects after excimer PRK surgery.

4.2 Posology and method of administration

Adults

Pre-operatively: 1 drop four times during the 2 hours before surgery.

Post-operatively: 1 drop four times daily for up to 12 weeks.

Post PRK pain: 1 drop 2 times in the hour prior to surgery, one drop 2 times five minutes apart immediately after PRK surgery and then post-operatively 1 drop every 2-5 hours while awake for up to 24 hours.

Other indications: 1 drop 4 to 5 times daily depending upon the severity of the disease.

Children

Paediatric Use: Voltarol Ophtha is not indicated for use in children. Paediatric experience is limited to a few published clinical studies in strabismus surgery.

Elderly

There is no indication that dosage needs to be modified for the elderly.

The dispenser remains sterile until the original closure is broken. Patients must be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures as this may contaminate the solution.

Following instillation of the eye drops, nasolacrimal occlusion or closing of the eyes for 5 minutes may reduce systemic absorption. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

Patients with known hypersensitivity to any of the ingredients.

Like other non-steroidal anti-inflammatory agents, Voltarol Ophtha is also contraindicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or by other drugs with prostaglandin synthetase inhibiting activity. Intraocular use during surgical procedure is also contraindicated.

4.4 Special warnings and precautions for use

The anti-inflammatory activity of ophthalmic non-steroidal anti-inflammatory agents (NSAIDs) including diclofenac may mask the onset and/or progression of ocular infections.

In the presence of infection, or if there is a risk of infection, appropriate therapy (eg antibiotics) should be given concurrently with Voltarol Ophtha Multidose.

Eye drops are not for injection. They should never be injected to subconjunctivally, nor should they be directly introduced into the anterior chamber of the eye.

Although there have been no reported adverse events, there is a theoretical possibility that patients receiving other medications which may prolong bleeding time, or with known haemostatic defects may experience exacerbation with Voltarol Ophtha Multidose.

Caution should be exercised when topical NSAIDs such as diclofenac are used concomitantly with topical steroids (see section 4.5 Interaction with other medicinal products and other forms of interaction).

This medicine contains 0.0014 mg benzalkonium chloride in each drop.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Patients should be advised to remove contact lenses before using this medicinal product and to wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use of topical NSAIDs such as diclofenac and topical steroids in patients with pre-existing corneal inflammation may increase the risk of developing corneal complications, therefore caution should be used. Ocular diclofenac at 0.1 % has been used safely in clinical studies in combination with beta-blockers e.g. timolol and antibiotics e.g. tobramycin for ocular use.

To prevent the active substances from being washed out when additional ophthalmic medication is used, an interval of at least 5 minutes between each application should be adhered to.

4.6 Fertility, pregnancy and lactation

Pregnancy

No reproductive toxicity studies have been conducted with Voltarol Ophtha Multidose.

Systematic diclofenac has been shown to cross the placental barrier in mice and rats, but had no influence on the fertility of parent animals in rats. There was no evidence that diclofenac had a teratogenic potential in routine mice, rat or rabbit embryo-foetal development studies. In rats, maternally toxic doses were associated with dystocia, prolonged gestation,

decreased foetal survival, and intrauterine growth retardation. The slight effects of diclofenac on fertility and delivery as well as constriction of the ductus arteriosus in utero are pharmacological consequences of this class of prostaglandin synthesis inhibitors.

The prenatal, perinatal and postnatal development of the offspring were not affected.

Animal studies to date have shown no risk to the foetus during the first and second trimesters of pregnancy but no controlled studies in pregnant women are available.

Voltarol Ophtha Multidose Eye Drops should not be used during the third trimester of pregnancy, due to a possible risk of premature closure of the ductus arteriosus and possible inhibitions of contractions.

Lactation

After oral administration of 50mg coated tablets (equivalent to 10 bottles of eye drops) only traces of diclofenac were detected in breast milk. The quantities were so small that no undesirable effects on the infant would be expected. Use of ocular diclofenac is not recommended during breast-feeding unless the expected benefits outweigh the possible risks.

4.7 Effects on ability to drive and use machines

Patients with blurred vision should refrain from driving a vehicle or operating machines.

4.8 Undesirable effects

The following adverse events have been reported:

Very frequent: Eye pain.

The other frequently observed adverse reaction is a transient, mild to moderate eye irritation.

Other less frequently observed reactions are eye pruritis, ocular hyperaemia and blurred vision immediately after instillation of the eye drops. Punctate keratitis or corneal disorders have been observed, usually after frequent application.

In patients with risk factors of corneal disorders such as during the use of Corticosteroids or with concomitant diseases such as infections or rheumatoid arthritis, diclofenac has been associated, in rare cases, with ulcerative keratitis, corneal thinning, punctuate keratitis, corneal epithelium defect and corneal oedema, which might become sight threatening. Most patients were treated for a prolonged period of time.

In rare cases dyspnoea and exacerbation of asthma have been reported.

Allergic conditions have been reported such as conjunctival hyperaemia, allergic conjunctivitis, eyelid erythema, eye allergy, eyelid oedema, eyelid pruritus, urticaria, rash, eczema, erythema, pruritus, hypersensitivity, cough and rhinitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 676 4971
Fax: +353 1 676 2517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

There is no experience of overdose with Voltarol Ophtha Multidose. However, accidental oral ingestion carries nominal risk of adverse effects, as a 5ml bottle of the eye drops contains only 5mg of diclofenac sodium, corresponding to about 3% of the recommended maximum daily adult dose of Voltarol after oral administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Voltarol Ophtha Multidose contains diclofenac sodium, a non-steroidal compound with pronounced anti-inflammatory and analgesic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a major role in the causation of inflammation and pain.

In clinical trials, Voltarol Optha has been found to inhibit miosis during cataract surgery, to reduce inflammation following surgical interventions and to reduce ocular pain and discomfort associated with corneal epithelial defects after excimer PRK surgery or accidental non-penetrating trauma. They also reduce the incidence of angiographic cystoid macular oedema after cataract surgery.

The effective daily dose after ocular application of Voltarol Ophtha Multidose (approximately 0.25 - 0.5 mg diclofenac sodium) corresponds to less than 1% of the daily dose recommended for Voltarol in rheumatic indications.

Voltarol Ophtha Multidose Eye Drops contain a cyclodextrin, hydroxypropyl γ-cyclodextrin (HPγ-CD). Cyclodextrins (CDs) increase the aqueous solubility of some lipophilic water-insoluble drugs. It is believed that CDs act as true carriers by keeping hydrophobic drug molecules in solution and delivering them to the surface of biological membranes.

5.2 Pharmacokinetic properties

In rabbits, peak concentrations of ^{14}C-labelled diclofenac could be demonstrated in the cornea and conjunctiva 30 minutes after application. The highest amounts are found in these two tissues and in the choroid and retina. Elimination was fast and almost complete after 6 hours.

Concentrations of HP-gamma-CD in plasma and aqueous humor were below detection limits (1 nMol/mL) in rabbits after single or four times daily (q.i.d.) ocular administration for 28 days. Low concentrations of HP-gamma-CD were detected in the aqueous humor of two rabbits (1 after single instillation, 1 after q.i.d. instillation for 28 days).

Penetration of diclofenac into the anterior chamber has been confirmed in humans. No measurable levels of diclofenac could be found in humans after ocular application of diclofenac sodium eye drops.

5.3 Preclinical safety data

Preclinical data of systemically applied diclofenac from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, teratogenicity, carcinogenicity and reproductive performance studies revealed no specific hazard for humans at the intended therapeutic doses. Systemic diclofenac has been shown to cross the placental barrier in mice and rats, but had no influence on the fertility of parent animals in rats. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, decreased foetal survival, and intrauterine growth retardation. The slight effects of diclofenac on fertility and delivery as well as constriction of the ductus arteriosus in utero are pharmacological consequences of this class of prostaglandin synthesis inhibitors.

Local ocular tolerance and toxicity of different formulations of Voltarol Ophtha were investigated and no evidence of toxicity and local adverse effects were found.

Voltarol Ophtha Multidose

The potential for local ocular toxicity and associated systemic toxicity of Voltarol Ophtha Multidose Eye Drops and HPγ-CD were investigated in a series of ocular tolerance studies in rabbits. In these studies the rabbits received up to 8 instillations of

25µl of solution into the conjunctival sac of the right eye each day for up to 13 weeks. The left eye was untreated and provided a control for local effects in the treated right eye.

The animals received either Voltarol Ophtha Multidose Eye Drops with or without benzalkonium chloride; a formulation containing the excipients of Voltarol Ophtha Multidose Eye drops but 0.1% diclofenac potassium instead of diclofenac sodium; a 2% solution of HPγ-CD in saline solution. In none of the studies was there any evidence of local adverse effects detectable by detailed ophthalmological and ocular histological examinations. There was no evidence of systemic effects in the haematology, clinical chemistry, urinalysis parameters or in the histological examination of the liver, lungs and kidneys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Hydroxypropyl γ-cyclodextrin
Hydrochloric acid
Propylene glycol
Trometamol
Tyloxapol
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years

Opened: 4 weeks.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

5ml white LDPE bottle with LDPE dropper and HDPE closure.

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

Laboratoires Thea
12, rue Louis Blériot
63017 Clermont-Ferrand Cedex 2
France

8 MARKETING AUTHORISATION NUMBER

PA1107/009/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/05/2002

Date of last renewal: 12/10/2008

10 DATE OF REVISION OF THE TEXT

September 2020