SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIFENASOL 0,1 % eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: 1mg/ml.sodium diclofenac.
Excipient with known effect:
Benzalkonium chloride (preservative)
-Acide borique .

3. PHARMACEUTICAL FORM

Eye drops solution.
Liquid clear to pale yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Inhibition of perioperative miosis during cataract surgery.
- Prevention of post-operative inflammation in cataract and eye anterior segment surgery (see section 5.1).
- Treatment of ocular pain during the 24 hours following photorefractive keratectomy surgery.

4.2 Posology and method of administration

Posology
Adults
- Inhibition of miosis during cataract surgery:
  - Preoperative: 1 drop up to 5 times during the 3 hours before surgery.

- Prevention of inflammation in cataract and eye anterior segment surgery:
  - Pre-operatively: 1 drop up to 5 times during the 3 hours before surgical intervention.
  - Post-operatively: 1 drop 3 times immediately after surgical intervention, then one drop 3 to 5 times daily. Treatment duration should not exceed 4 weeks.

- Treatment of ocular pain during the 24 hours following photorefractive keratectomy surgery:
  - Pre-operatively: 2 drops in the hour prior to surgery.
  - Post-operatively: 2 drops immediately after surgery and then 4 drops during the 24 post-operative hours.

Paediatric use
No specific studies for use in children were conducted.

Elderly patients
In these patients no dose adjustment is required.

Method of administration
Ocular use.

Patients should be advised to:

- Carefully wash hands before using the drops.
- Avoid any contact between the nozzle and the eye or eyelid.
- Recap the bottle after use.

Following instillation of the eye drops, nasolacrimal occlusion and closing the eyes for 2 minutes may reduce the systemic absorption. This allow to decrease systemic side effects and increase in local activity (see section 4.4).

In case of concomitant use with other eye drops, an interval of 15 minutes between each application should be maintained to prevent the dilution of active substances. Ointments should be administered last.

1. With the spike: tighten the cap on the nozzle.
2. The spike in the cap will pierce the tip of the bottle.
3. Dispense drops with gentle pressure.

Replace the cap after every use.

4.3 Contraindications

Known hypersensitivity to the active substance (diclofenac sodium) or to any of the excipients mentionned in section 6.1.

History of allergy, urticaria, acute rhinitis or asthma triggered by diclofenac sodium intake or by other drugs with a similar activity, such as aspirin and the other non steroidal anti-inflammatory drugs (NSAIDs) (see section 4.4 regarding cross hypersensitivity reactions).

Pregnancy, from the beginning of the 6th month (after 24 weeks of amenorrhea) (section 4.6).

4.4 Special warnings and precautions for use

Do not inject, do not swallow.

This eye drops solution is not intended for peri ocular or intra ocular injection.

Hypersensitivity
Difénasol, as others NSAIDs, may induce in rare cases allergic reactions including anaphylactic reactions, even without prior exposure to the drug.
In case of hypersensitivity reactions such as itching, redness or signs suggesting allergy including asthma attack or sudden swelling of the face and the neck, the treatment should be discontinued.

Corneal diseases
Topical NSAIDs, such as diclofenac in local use, may delay corneal epithelium healing even when there are used during a short time period. The consequences of delayed corneal healing on the cornea quality and on the risk of infection are not clear.

Topical corticosteroids are also known to slow down and delay healing. The concomitant use of topical steroids with topical NSAIDs may increase the risk of problems during healing.

When patients are treated with high doses for a prolonged period of time, topical NSAIDs may induce keratitis. In some sensitive patients, the continuous use of topical NSAIDs may lead to rupture of epithelium barrier, corneal thinning, corneal infiltrate, corneal epithelium defect, corneal ulcers and corneal perforation. These events can be sight-threatening. Patients presenting corneal epithelium damage signs should discontinue immediately the use of Difénasol and the condition of the cornea should be carefully monitored.

Post marketing experience of the medicine indicates that patients with epithelium abnormalities, diabetes, ocular surface condition (e.g. dry eyes), rheumatoid arthritis or complex eye surgery or repetitive eye surgeries in a short timeframe can present an increase risk of corneal undesirable effects
The local NSAIDs should be use with caution in these patients. Prolonged use of local NSAIDs can increase risk of corneal appearance and gravity side effects.

Ocular infection
The anti-inflammatory activity of ophthalmic NSAIDs may mask the onset and/or progression of ocular infections. NSAID has no antimicrobial properties. In case of ocular infection, caution should be exercised when topical NSAIDs are used concomitantly with antibiotics.

Hypersensitive population
Compared to the rest of the population, patients with simultaneous asthma and chronic rhinitis, chronic sinusitis and/or nasal polyps conditions present an increased incidence of allergic reactions when taking aspirin and/or NSAIDs.
NSAIDs can increase the extent of bleeding of ocular tissues during the surgery. It is advised to used the eye drops with caution in patients with bleeding tendency or treated with blood thinners.

Crossed sensitivity
Allergic crossed reactions with salicylic acid and other NSAIDs are possible (see section 4.3).

Contact lenses
Wearing soft contact lenses is not recommended after cataract surgery. Patients should therefore be advised not to wear contact lenses unless clearly instructed by their physician to do so.

Excipient
Difenasol contains benzalkonium, it may cause eyes irritation.
Difenasol contains boron in the form of boric acid, this medicine should not be given to a child under 2 years of age, it may affect their future fertility.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies are available.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandins synthesis by the NSAIDs can affect the course of the pregnancy and/or the development of the embryo or foetus.

Risk associated with the use during the 1st trimester
Epidemiological studies data suggest an increase of miscarriage, cardiac malformations and gastroschisis, after a treatment with an inhibitor of prostaglandins synthesis in the beginning of the pregnancy. The absolute risk of cardiovascular malformation was from 1 % in the general population to approximately 1,5 % in patients exposed to NSAIDs. The risk seems to increase depending on the dose and the treatment duration. In animals, it was shown that the administration of inhibitor of prostaglandins synthesis would cause an acute loss pre and post implantation and an augmentation of the embryo-foetal lethality. In addition, a superior incidence of certain malformations, included cardiovascular one, was reported in animals that received inhibitors of prostaglandins synthesis during the gestational organogenesis phasis.

Risk associated with the use during the 12th weeks of absence of menstruation until birth
From the 12th week of absence of menstruation and until the birth, all the NSAIDs, by inhibition of the prostaglandin synthesis, could expose the foetus to **a renal functional damage :**

- *in utero* can be observed from 12 weeks (starting of the foetal diuresis): oligohydramnios (most of the time reversible when treatment discontinued), or anamnios in particular when prolonged exposition.
- At birth, renal failure (reversible or not) can persist in particular in case of late exposition or prolonged (with a risk of a delayed severe hyperkalaemia).

Risk associated with the use after the 24th weeks of absence of menstruation until birth
After the 24th weeks of absence of menstruation, NSAIDs can expose the foetus to a **cardiopulmonary toxicity** (early closure of the arterial canal and arterial pulmonary hypertension). The constriction of the arterial canal can happen at the beginning of the 6th month (after the 24th weeks of absence of menstruation) and can lead to right foetal or neonatal cardiac failure or in utero foetal death. This risk is more serious closer when the intake is closer to delivery (less reversibility). This effect exists even for a single intake.

End of pregnancy, the mother and the new-born can present
- Prolonged bleeding time due to the antiaggregant action that could happen even with small doses of the medicine.
- Inhibition of uterine contractions leading to a delay of the term of the pregnancy or the prolonged birth delivery.

In consequence
Except critical necessity, this medicine should not be prescribe to women who is planning to have a baby or during the five first months of pregnancy (24 weeks of absence of menstruations). If this medication is administered to a women planning to have a baby or pregnant for less than 5 months, the dose will have to be the lowest possible and the treatment duration the shortest possible. Prolonged intake is strongly discouraged.

Starting from the 6th month (after 24 weeks without menstruations) : every intake even once is contraindicated. An inadvertently intake from this date justify a cardiac and renal monitoring, foetal and/or neonatal depending the pregnancy term exposition. The duration of monitoring will be adapted to the half life of the molecule.

Breast-feeding

No effect are expected in the child breastfed because the systemic exposition of the mother breastfeeding to diclofenac sodic is limited after ocular application. Difénasol can be used during breastfeeding.

Fertility

As all NSAIDs, the utilisation of this medicine can temporarily alter the female fertility, on the ovulation process. Therefore it is not recommended to women planning to have a baby. In women struggling to conceive or performing sterility tests, the discontinuation of the treatment should be considered

4.7 Effects on ability to drive and use machines

A transient blurred vision may occur immediately after instillation of Difénasol. Patients with blurred vision should refrain from driving a vehicle or operating machines.

4.8 Undesirable effects

Infections and infestations
Not known frequency (can't be determined on available database): rhinitis.

Immune system disorders
Rare (≥1/10,000, <1/1000): hypersensitivity.

Eye disorders:

Uncommon (≥1/1000, <1/100): a slight transient burning sensation and blurred vision immediately after instillation of eye drops.

Rare (≥1/10,000, <1/1000): punctate keratitis, corneal thinning, and ulcerative keratitis.
Not known frequency (can't be determined on available database): conjunctival hyperhaemia, allergic conjunctivitis, eyelid oedema.

Respiratory, thoracic and mediastinal disorders
Rare (≥1/10,000, <1/1000): dyspnea and exacerbation of asthma.
Not known frequency (can't be determined on available database): cough.

Skin and subcutaneous tissue disorders
Rare (≥1/10,000, <1/1000): pruritis, erythema, hypersensitivity reactions.
Not known frequency (can't be determined on available database): urticaria, rash, eczema.

In patients with risk factors of corneal disorders such as during the use of corticosteroids or with concomitant rheumatoid arthritis, diclofenac has been associated, in rare cases, with corneal thinning, corneal ulcers. Most patients were treated for a prolonged period of time (see section 4.4).
As benzalkoniulm chloride is present, there is a risk of eye irritation.

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 the national reporting system.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinflammatory agents, non steroids, ATC code: S01BC03.

Diclofenac sodium is an inhibitor of the prostaglandin synthesis enzyme. Diclofenac sodium has anti-inflammatory and analgesic properties.
Efficacy and security of eye-drops diclofenac in glaucoma filtering surgery are supported by a limited number of data.

5.2 Pharmacokinetic properties

In rabbits, peak concentrations of 14C-labelled diclofenac are achieved in the cornea and conjunctiva 30 minutes after application. Elimination was fast and almost complete after 6 hours.

Penetration of diclofenac into the anterior chamber has been confirmed in humans.

No measurable blood levels of diclofenac could be found in humans after ocular application of diclofenac sodium eye drops.

5.3 Preclinical safety data

During repeated dose toxicity studies, the most frequently observed adverse effects were gastrointestinal disorders, such as ulcerations, at oral dosage of 0,5 to 2,0 mg/kg according to species (namely 300 to 1200 times the ocular daily dose in humans).

In reproductive toxicity studies in animals, embryo-foetotoxicity, prolonged gestationand dystocia have been observed. Whilst no teratogenic effects have been demonstrated, maternally toxic dose were associated with decreased foetal survival, and intrauterine growth retardation.
Diclofénac did not show having mutagenic nor carcinogenic potential.

After up to 3 months of repeated instillations of diclofenac 1mg/ml in rabbits eyes, no adverse effect has been observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid, disodium edetate, benzalkonium chloride, polyoxyl-35 castor oil, tromethamine, water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Protect from light.
Do not use after one month after opening the bottle.
Keep out of the sight and reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Bottle of 5 ml made of LDPE (low density polyethylene).

6.6 Special precautions for disposal and handling

Not applicable.

7. CATEGORY OF DISTRIBUTION:

☐ Over-the counter medicine ☒ Prescription only medicine

List II

8. MARKETING AUTHORISATION HOLDER

Exphar sa
Zoning Industriel Sud – Zone 2
Avenue Thomas Edison, 105
1402 Thines
Belgium

9. MANUFACTURER

AHLCON PARENTERALS (INDIA) Ltd.
SP-917-918, Phase-III, Industrial Area
Bhiwadi 301019 - District Alwar (Rajasthan),
India

10. DATE OF REVISION OF THE TEXT

July 2022.