PREScribing INFORMATION

Pr VOLTAREN OPHTHA*

(Diclofenac Sodium)

0.1% w/v Ophthalmic Solution

Anti-inflammatory Analgesic Agent

Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec
H9S 1A9

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*Voltaren Ophtha is a registered trademark
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PART 1: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Ophthalmic</td>
<td>Ophthalmic solution</td>
<td>Multi-dose bottles: Sorbic Acid 0.2% Preservative</td>
</tr>
<tr>
<td></td>
<td>diclofenac sodium 0.1%</td>
<td>For a complete listing see Dosage Forms, Composition and Packaging section.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

VOLTAREN OPHTHA* (diclofenac sodium 0.1%) ophthalmic solution is indicated for the following conditions of the eye:

- Post-operative inflammation after cataract surgery
- Non-chronic post-traumatic inflammation in non-penetrating wounds

Pediatrics (under 18 years of age):
The safety and dosage ranges of VOLTAREN OPHTHA* have not been established in children under 18 years of age. VOLTAREN OPHTHA* is not indicated for use in children.

CONTRAINDICATIONS

Known hypersensitivity to (diclofenac sodium) or any component of the medication.

Since there exists the potential for cross-sensitivity, VOLTAREN OPHTHA* should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents.
WARNINGS AND PRECAUTIONS

General
The anti-inflammatory and analgesic effects of VOLTAREN OPHTHA* may mask signs of infection and physicians should be alert to the development of infection and closely monitor patients receiving the drug.

In the presence of infection or if there is a risk of infection, appropriate therapy (antibiotics) should be given concurrently with VOLTAREN OPHTHA*.

Hematologic
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 hemostatic defects may experience exacerbation with VOLTAREN OPHTHA*.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.

Ophthalmologic
All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs such as VOLTAREN OPHTHA* and topical steroids may increase the potential for healing problems. It should also be noted that concomitant use of VOLTAREN OPHTHA* and topical corticosteroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications. The concomitant use of diclofenac sodium with topical corticosteroids should be undertaken with caution. [See Drug-Drug Interactions]

Post-marketing experience with topical NSAIDs suggests that patients experiencing complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface disease (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events (keratitis, epithelial breakdown, corneal thinning, corneal infiltrates, corneal erosion, corneal ulceration, and corneal perforation), these events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health. Topical NSAIDs such as VOLTAREN OPHTHA* should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggest that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events.

It is recommended that physicians conduct periodic examinations of the eye, including measurement of intraocular pressure. A slight and transient elevation in the intraocular pressure
(IOP) has been observed in some patients, following surgery, even with the use of VOLTAREN OPHTHA*.

Soft contact lenses should not be worn during treatment. The lenses must be removed before application of the drops and not reinserted earlier than 15 minutes after use.

**Special Populations**

**Pregnant Women:**
The safety of VOLTAREN OPHTHA* (diclofenac sodium) in pregnancy has not been established and its use is therefore not recommended in pregnant women, unless the potential benefit to the mother outweighs the possible risk to the child.

**Nursing Women:**
The safety of VOLTAREN OPHTHA* (diclofenac sodium) in lactation has not been established and its use is therefore not recommended in lactating women, unless the potential benefit to the mother outweighs the possible risk to the child.

**Geriatrics (over 65 years of age):**
VOLTAREN OPHTHA* was well tolerated by patients presenting with post-traumatic ocular inflammatory conditions and inflammatory responses of the eye resulting from surgical intervention for cataracts, including elderly patients with senile cataracts requiring lens extraction and re-implantation.

**Pediatrics (under 18 years of age):**
The safety and dosage ranges of VOLTAREN OPHTHA* have not been established in children under 18 years of age. VOLTAREN OPHTHA* is not indicated for use in children.

**ADVERSE REACTIONS**

**Adverse Drug Reaction Overview**

The most frequently observed adverse reaction is a transient, mild to moderate eye irritation in the eye.

Other less frequently observed reactions are eye pain, eye pruritus, ocular hyperemia and blurred vision immediately after instillation of the eye drops.

Punctate keratitis or corneal disorders have been observed, usually after frequent application.

In rare cases dyspnoea and exacerbation of asthma have been reported.
Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

When instilled into the eye, VOLTAREN OPHTHA* has been associated with a mild to moderate burning sensation in 5 to 15% of patients studied. This symptom was transient in nature and almost never necessitated discontinuation of treatment. In addition, there has been one report each of the following symptoms: sensitivity to light, bad taste, feeling of pressure and a stainable cornea. There have also been 2 reports of an allergic reaction. The incidence of these latter five symptoms was 0.2 to 0.3% of all patients studied.

In cataract surgery studies, keratitis was reported in up to 28% of patients receiving VOLTAREN OPHTHA*, although in many of these cases keratitis was initially noted prior to the initiation of treatment.

Elevated intraocular pressure following cataract surgery was reported in approximately 15% of patients undergoing cataract surgery.

Lacrimation complaints were reported in approximately 30% of cases studies undergoing incisional refractive surgery.

The following adverse reactions were reported in approximately 5% or less of the patients: abnormal vision, acute elevated IOP, blurred vision, conjunctivitis, corneal deposits, corneal edema, corneal opacity, corneal lesions, discharge, eyelid swelling, injection, iritis, irritation, itching, lacrimation disorder and ocular allergy.

The following adverse reactions were reported in 3% or less of the patients: Abdominal pain, asthenia, chills, dizziness, facial edema, fever, headache, insomnia, nausea, pain, rhinitis, viral infection, and vomiting.

Post-Market Adverse Drug Reactions

In patients with risk factors for corneal disorders such as during the use of corticosteroids or with concomitant diseases such as infections, rheumatoid arthritis, diclofenac has been associated, in rare cases, with ulcerative keratitis, corneal thinning, punctuate keratitis, corneal epithelium defect and corneal edema, which might become sight-threatening.

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

Drug-Drug Interactions
Concomitant use of topical NSAIDs such as VOLTAREN OPHTHA* and topical steroids may increase the potential for healing problems. It should also be noted that concomitant use of VOLTAREN OPHTHA* and topical corticosteroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications. The concomitant use of diclofenac sodium with topical corticosteroids should be undertaken with caution.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Cataract surgery procedures:
Pre-operatively: instill 1 drop in the conjunctival sac up to 5 times during the 3 hours preceding surgery.
Post-operatively: instill 1 drop in the conjunctival sac 15, 30 and 45 minutes following surgery, then 3 to 5 times daily, for up to 4 weeks.

Non chronic post-traumatic inflammation in non-penetrating wounds:
Instill 1 drop in the conjunctival sac 4 to 5 times daily, depending upon the severity of the disease. Eye swab for culture should be taken before initiation of therapy.

Administration

In surgery, VOLTAREN OPHTHA* has been combined with such standard pretreatment measures as mydriatics and topical antibiotics.

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

OVERDOSAGE

There has been limited experience with diclofenac sodium overdose, even when given systemically. The risk of an acute toxic response is highly remote, as a 5 mL bottle of VOLTAREN OPHTHA* contains a total of only 5 mg diclofenac sodium, equivalent to just 3% of the normal recommended oral adult dose.

If VOLTAREN OPHTHA* is accidentally ingested, fluids should be taken to dilute the medication.

For management of a suspected drug overdose, contact your regional Poison Control Center.
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Diclofenac sodium is a nonsteroidal anti-inflammatory drug with analgesic properties. The mode of action is not fully known, but it does not act through the pituitary-adrenal axis, even when given systemically. Diclofenac sodium inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. Prostaglandins play a critical role in many inflammatory processes of the eye and appear to play a role in the miotic response during ocular surgery. Topically applied diclofenac sodium significantly reduces prostaglandin-synthetase activity in inflamed eyes, but does not appear to suppress the immune system.

Pharmacodynamics
In clinical studies VOLTAREN OPHTHA* has been found to inhibit miosis during cataract surgery, to reduce inflammation following surgical interventions, trauma, and in other non-infected inflammatory conditions. VOLTAREN OPHTHA* reduced the frequency and intensity of cystoid macular edema when administered prophylactically to patients undergoing cataract lens extraction with intraocular lens implantation.

Epithelialization was not adversely affected or delayed. A slight and transient elevation in the intraocular pressure (IOP) has been observed in some patients, following surgery, even with the use of VOLTAREN OPHTHA*.

Pharmacokinetics
In man, the drug promptly passed into the aqueous humour following the topical application of 3-16 drops of 0.1% diclofenac sodium to the eye. Levels of unchanged diclofenac in the aqueous humour were highly variable, ranging from 10 to 505 ng/g. There were no detectable levels of drug in plasma, indicating that no measurable systemic absorption occurs following a single instillation of the ophthalmic drops.

STORAGE AND STABILITY
Storage:
VOLTAREN OPHTHA* (diclofenac sodium) 0.1% ophthalmic solution in bottles should be stored at 15° to 30° C and protected from light. Single-dose units should be stored at 25°C.

Others:
Keep in a safe place out of reach of children.

SPECIAL HANDLING INSTRUCTIONS
Not applicable.
DOSAGE FORMS, COMPOSITION AND PACKAGING

VOLTAREN OPHTHA* (diclofenac sodium) 0.1% ophthalmic solution is available in dropper bottles of 2.5 mL, 5 mL and 10 mL preserved with sorbic acid. Unpreserved VOLTAREN OPHTHA* is available in single dose units (0.3 mL).

Composition:

- Active ingredient: Diclofenac sodium
- Non-Medical ingredients:
  - Preserved multi-dose bottles:
    - Cremophor EL,
    - Boric acid,
    - Tromethamine (TRIS),
    - Sorbic Acid,
    - Edetate Disodium,
    - Purified water
  - Unpreserved single dose units:
    - Cremophor EL,
    - Boric acid,
    - Tromethamine (TRIS),
    - Purified water
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Brand name: VOLTAREN OPHTHA*

Proper name: Diclofenac sodium

Chemical name: Sodium O-[(2,6-dichlorophenyl) amino] phenylacetate

Molecular formula and molecular mass: C_{14}H_{10}Cl_{2}NO_{2}Na, 318.5

Structural formula:

![Structural formula of Diclofenac sodium]

Physicochemical properties:

Description:

Diclofenac sodium is a white to off-white powder, with a salty bitter taste. At 25°C, diclofenac sodium is 2% soluble in water (pH 7.7). It is practically insoluble in aqueous acidic solutions.
CLINICAL TRIALS

VOLTAREN OPHTHA* has been studied in the treatment of post-traumatic inflammation resulting from non-penetrating wounds and as a prophylactic treatment against inflammatory responses of the eye resulting from cataract surgery.

Post-traumatic inflammations of the eye responded promptly to VOLTAREN OPHTHA* and re-epithelialization was not delayed.

Inflammations of the eye are associated with 4 major target symptoms: conjunctival injection, ciliary injection, pain and corneal involvement. These symptoms were regularly monitored in a series of 147 patients presenting with acute and chronic inflammatory conditions. Within 4-5 days of the start of VOLTAREN OPHTHA* therapy, from 90 to 96% of these patients showed considerable improvement. Among these same patients, 96% were considered clinically cured after an average of 4-15 days of VOLTAREN OPHTHA* treatment.

VOLTAREN OPHTHA* proved to be equally useful as a post-operative anti-inflammatory agent in patients undergoing cataract surgery. In general, VOLTAREN OPHTHA* treatment was initiated 3-4 hours prior to surgery and was continued post-operatively (up to 4 weeks) at the usual anti-inflammatory dose as required.

VOLTAREN OPHTHA* was effective in reducing or eliminating such post-operative inflammatory responses as anterior chamber turbidity, corneal edema, elevated protein levels, ciliary injection and conjunctival hyperaemia. In addition, post-operative pain was consistently reduced. VOLTAREN OPHTHA* was also associated with a significant anti-miotic effect, which was apparent during the surgery itself, as well as during the first post-operative day.

VOLTAREN OPHTHA* was well tolerated by patients presenting with post-traumatic ocular inflammatory conditions and inflammatory responses of the eye resulting from surgical intervention for cataracts, including elderly patients with senile cataracts requiring lens extraction and re-implantation. Of the more than 500 patients who participated in clinical trials of VOLTAREN OPHTHA*, 5 to 15% complained of mild transient burning at the time of instillation. Treatment did not have to be interrupted for reasons of either intolerance or poor patient acceptance.
DETAILED PHARMACOLOGY

Diclofenac sodium is a phenyl-acetic acid derivative possessing anti-inflammatory, analgesic and antipyretic activities as shown in various pharmacological models.

Anti-inflammatory Activity

Rats: Oral Administration

The anti-inflammatory potency was assessed by testing inhibition of paw edema (carrageenin solution and kaolin suspension) and reduction of adjuvant arthritis (Freund's adjuvant).

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Carrageenin (ED₅₀ mg/kg p.o.)</th>
<th>Kaolin (ED₅₀ mg/kg p.o.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac sodium</td>
<td>2.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* Determined by graphic interpolation from 3 or more doses

Rats: Topical Administration to the Eye

Ocular inflammations were induced in rats using various chemical agents, including carrageenin, formalin, albumin, yeast and mustard. Diclofenac sodium 0.1% was instilled in the eye at various times up to 4 hours prior to chemical challenge. The percent maximum inhibition of chemically-induced edema by diclofenac sodium was superior to most nonsteroidal anti-inflammatory agents, including the standard, indomethacin.

<table>
<thead>
<tr>
<th>Irritant</th>
<th>0.1% diclofenac % Inhibition</th>
<th>0.1% indomethacin % Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenin</td>
<td>31.9%</td>
<td>Not available</td>
</tr>
<tr>
<td>Yeast</td>
<td>29.2%</td>
<td>21.2%</td>
</tr>
<tr>
<td>Albumin</td>
<td>24.4%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Mustard</td>
<td>20.7%</td>
<td>19.6%</td>
</tr>
</tbody>
</table>

Rabbits: Topical Administration to the Eye

Ocular Paracentesis

Following primary anterior chamber paracentesis, the rabbit eye becomes congested and there is protein influx into the aqueous humour. Paracentesis-induced ocular irritation in rabbits, therefore, is a good model for the study of ophthalmic anti-inflammatory agents.
When rabbits were pre-treated with 0.1-1% diclofenac sodium 30 minutes prior to paracentesis, the rise in aqueous humour proteins was attenuated by up to 85%. This response was comparable to that obtained with indomethacin and demonstrated that the drug penetrates the iris in levels sufficient to interfere with the prostaglandin mediated effects in the anterior chamber.

Other groups of rabbits were pre-treated with 1 drop of diclofenac sodium (3 x 10^{-6} to 3 x 10^{-2} M) 15-30 minutes before paracentesis. A second paracentesis was performed 30 minutes after the first in order to establish both a primary and secondary inflammation. A dose-related inhibitory effect of the protein influx was observed, which reached 100% with the higher doses. The optimal effect was reached with 100-300 nmol/mL and the ID_{50} was 5.4 nmol/eye (equivalent to 0.0017%). This inhibitory effect was slightly more potent than that achieved with indomethacin.

0.01% diclofenac sodium drops were compared to the vehicle in rabbits pre-treated with 1 drop of the anti-inflammatory prior to challenge. The mean inhibition of the paracentesis-induced protein influx was 72 ± 7% which compared very favourably to indomethacin and was superior to other nonsteroidal anti-inflammatory agents tested. The effectiveness of diclofenac sodium was related to its high degree of lipid solubility, which enhances penetration to the intraocular tissues.

A time course of the inhibitory effect was also determined by increasing the length of the interval between the instillation and paracentesis. The half-life of the inhibitory effect was approximately 10 hours.

In another group of rabbits subjected to primary and secondary paracentesis, the anti-inflammatory effect was determined by measuring the protein concentration in the aqueous humour, the leukocyte count, intraocular pressure (IOP) and pupil diameter. One hour prior to the first paracentesis, a volume of 50 \mu l of diclofenac sodium was instilled in concentrations of 0-20 mM. Concentrations above 2 mM significantly reduced protein concentrations, leukocyte accumulations in the secondary aqueous and IOP (p<0.001), but had no anti-miotic effect.

In a study in which primary paracentesis was followed by chemically-induced leukotaxis, various concentrations of diclofenac sodium drops were instilled prophylactically 1 hour prior to paracentesis. At concentrations ≥ 0.064%, diclofenac sodium decreased both protein concentrations and leukocyte accumulations in the aqueous humour and strongly inhibited the increase in IOP.

**Endotoxin-induced Uveitis**

Uveitis was induced in rabbits by injecting *Shigella* endotoxin into the centre of the vitreous humour of each eye. Fifteen minutes before the endotoxin injection, the animals were pre-treated with 10 \mu l diclofenac sodium in concentrations ranging from 0.0625 to 1% or with the vehicle alone to serve as control. Subsequent instillations were made 5, 12 and 23 hours after the challenge. At concentrations up to 0.25%, diclofenac sodium drops significantly inhibited the leukocyte influx and prostaglandin synthetase activity (p<0.01) and reduced the protein content.
in the aqueous humour (p<0.05). The optimum concentration was 0.25%; higher concentrations apparently induced an irritant effect of their own.

Uveitis has also been induced in the rabbit eye by injecting bovine serum albumin into the vitreous humour. After recovery, the animals were re-challenged with an i.v. injection of 10 mg/kg bovine serum albumin to produce a secondary response. Groups of animals received either 100 $u$1 of 0.25% diclofenac sodium or 0.5% indomethacin applied to the cornea 3 times over 24 hours, starting 30 minutes before the i.v. challenge. Another group received diclofenac sodium drops, 100 $u$1 t.i.d. for 48 hours starting 24 hours after the i.v. challenge.

Diclofenac sodium drops were effective in significantly reducing the ocular reaction to the immunological response when given either before or after the challenge. By contrast, protein and leukocyte concentrations were only slightly affected by indomethacin. Both diclofenac and indomethacin inhibited prostaglandin synthetase activity (p<0.05), which was significantly elevated over the normal values by the intervention.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eye†</th>
<th>Protein (mg/mL)</th>
<th>Leukocyte (/cu mm)</th>
<th>PG-formation (ng/iris/30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>T</td>
<td>16.5 ± 6.6*</td>
<td>2518 ± 583*</td>
<td>2.9 ± 1.1*</td>
</tr>
<tr>
<td>Diclofenac Na</td>
<td>C</td>
<td>36.2 ± 6.9</td>
<td>6532 ± 933</td>
<td>28.1 ± 7.8</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>T</td>
<td>25.5 ± 5.5**</td>
<td>2396 ± 336*</td>
<td>47.5 ± 13.1*</td>
</tr>
<tr>
<td>Diclofenac Na</td>
<td>C</td>
<td>25.3 ± 3.8</td>
<td>3638 ± 518</td>
<td>91.7 ± 17.9</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>T</td>
<td>18.8 ± 3.7</td>
<td>6845 ± 2346</td>
<td>27.0 ± 4.4*</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>C</td>
<td>15.1 ± 2.3</td>
<td>8883 ± 1954</td>
<td>85.6 ± 16.2</td>
</tr>
</tbody>
</table>

†T=treated eye  C=control  *p<0.05  **p<0.01
All values expressed as mean ± SEM

**Experimental Alkali Burns of the Eye**

Diclofenac sodium drops (1.0%), indomethacin drops (0.5%) or vehicle were instilled into the eyes of rabbits which had received mild alkali burns to the anterior segment. The drops were instilled 3 times daily and the animals were monitored every 4 days for 12 days. Both active drugs substantially reduced vascularization of the cornea and intravascular injection. Lactate and glucose levels of the corneal stroma were sharply reduced, revealing that disturbances of the blood aqueous humour were normalized and that leukocyte concentrations were reduced.
Corneal Regeneration
The corneal epithelium was removed from the eyes of 3 groups of rabbits. One group was treated with 2-4 drops of 0.1% diclofenac sodium daily for 7 days, while the second group received vehicle only and the third group received no treatment. At the end of the treatment period, regeneration of the corneal epithelium was complete in all 3 groups. The animals receiving the vehicle healed the fastest, while those receiving no treatment were the slowest. It was therefore concluded that the diclofenac sodium drops slightly delayed but did not inhibit corneal re-epithelialization.

The results were corroborated in another study in which rabbits underwent a partial corneal de-epithelialization. Diclofenac sodium drops (0.01%, 0.1% and 0.5%) effectively inhibited polymorphonuclear leukocyte release into the tear fluid, but did not affect the rate of corneal regeneration.

Guinea Pigs: Topical Administration to the Eye
Virus-induced Keratitis
Guinea pigs were injected with Herpes simplex virus type 1, in order to induce severe conjunctivitis and keratitis. Two groups of animals received 5 daily instillations of either 0.1% diclofenac sodium or dexamethasone phosphate drops from days 3-10 after the inoculation. Two other groups received either the vehicle solution or no treatment at all.

None of the treatments was effective in reducing HSV-induced conjunctivitis, suggesting that this may not be a prostaglandin-mediated condition.

Anti-miotic Activity
Rabbits: Surgically-induced Miosis
The anti-miotic effect of 0.1% diclofenac sodium and 0.1% atropine eye drops was studied in groups of rabbits undergoing paracentesis of the anterior chamber. Two groups of animals received either the diclofenac or atropine drops alone at intervals starting 2 hours prior to surgery. A third group received a combination of both active drugs (atropine being instilled 5 minutes after each diclofenac application) and a fourth group received a saline solution as a placebo control. The diameter of the pupil was measured with a surgical compass.

Diclofenac sodium alone was effective in inhibiting the surgically-induced miotic response, with significant contralateral effects. Atropine also showed a strong anti-miotic effect, but with no contralateral effect. When the two drugs were combined, diclofenac sodium appeared to enhance the effect of atropine.

Prostaglandin Inhibition
A close correlation exists between certain febrile reactions and increased prostaglandin levels in the brain. Diclofenac (0.5 u g/mL) reduced prostaglandin E₂ formation, which parallels antipyresis, but does not induce hypothermia in the afebrile animal. The inhibition of prostaglandin synthesis in vitro (IC₅₀ u M/L) was 1.6.
Platelet Adhesiveness
At 15 u g/mL, diclofenac reduced collagen-induced aggregation in rabbit platelets by 50%. ADP-induced adhesiveness at the same dosage was similarly affected. At 10 mg/kg p.o., diclofenac protected rabbits against the lethal action of thrombokinase without untoward effects.

Pharmacokinetics
Following a single subconjunctival instillation of 0.5 mL of 0.1% diclofenac sodium in rabbits, levels of unchanged diclofenac could be detected in the aqueous humour from 1 to 4 hours after administration. The mean maximum concentration of 649 ng/g occurred 2 hours after administration; at 4 hours, the mean concentration of the drug in the aqueous humour was 45 ng/g.

Rabbits were given a single 50 u l application of 50 u g 14C-labelled diclofenac sodium in both eyes. The external tissues in direct contact with the solution, the cornea and conjunctiva, showed the highest concentrations of the drug, reached 30 minutes after application. The drug penetrated the cornea and was found in measurable levels in all the tissues of the eye for at least 6 hours. The difference in concentration between the external and intraocular tissues was about one order of magnitude. Small concentrations of diclofenac sodium were also absorbed into the bloodstream and could be detected in the blood up to 6 hours after topical application.

Mean Concentrations of diclofenac sodium in blood and ocular tissues of rabbits after topical application of 50 ug per eye

<table>
<thead>
<tr>
<th>Tissue*</th>
<th>Time Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 hour</td>
</tr>
<tr>
<td>Blood</td>
<td>0.053</td>
</tr>
<tr>
<td>Cornea</td>
<td>8.366</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>4.722</td>
</tr>
<tr>
<td>Nictitating Mem.</td>
<td>2.814</td>
</tr>
<tr>
<td>Ciliary body</td>
<td>0.564</td>
</tr>
<tr>
<td>Sclera</td>
<td>0.470</td>
</tr>
<tr>
<td>Choroid/retina</td>
<td>0.451</td>
</tr>
<tr>
<td>Iris</td>
<td>0.358</td>
</tr>
<tr>
<td>Aqueous humour</td>
<td>**</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>0.071</td>
</tr>
<tr>
<td>Vitreous humour</td>
<td>0.025</td>
</tr>
<tr>
<td>Lens</td>
<td>0.014</td>
</tr>
</tbody>
</table>

*Concentrations expressed as u g/g **Not available
In man, the drug promptly passed into the aqueous humour following the topical application of 3-16 drops of 0.1% diclofenac sodium to the eye. Levels of unchanged diclofenac in the aqueous humour were highly variable, ranging from 10 to 505 ng/g.

There were no detectable levels of drug in plasma, indicating that no measurable systemic absorption occurs following a single instillation of the ophthalmic drops.

**MICROBIOLOGY**
Not applicable.

**TOXICOLOGY**

*Acute Toxicity*

The acute oral toxicity of the 0.1% diclofenac sodium ophthalmic solution was studied in rats and mice. A single oral dose was administered by gavage with the following results:

<table>
<thead>
<tr>
<th>Species</th>
<th>Volume Diclofenac-Na (mL/kg)</th>
<th>Dose Equivalent (mg/kg)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice (Males &amp; Females)</td>
<td>5</td>
<td>5</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>50</td>
<td>7/10</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>30</td>
<td>3/15</td>
</tr>
<tr>
<td>Rats (Males &amp; Females)</td>
<td>30</td>
<td>30</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>50</td>
<td>1/10</td>
</tr>
</tbody>
</table>

The oral LD$_{50}$ in mice was calculated to be 103.8 mg/kg in females and between 30 and 50 mg/kg in males. Signs of toxicity were ptosis, reduced motor activity and diarrhea.

In rats, the maximum oral dose was limited by the volume of solution which could be administered. 50% mortality was not achieved and the LD$_{50}$ is considered to be >50 mg/kg. Signs of toxicity in rats were salivation, hypothermia, reduced motor activity and cachexia.

*Long Term Toxicity*

**General Toxicity of Diclofenac Sodium**

Male and female rats have been treated with diclofenac sodium orally for 59 to 98 weeks in doses ranging from 0.25 to 2.0 mg/kg/day. Ulceration of the gastrointestinal tract occurred in a
dose-dependent manner. However, bodyweight gains and feed consumption of the treated groups were similar to that of the controls. Haematologic patterns showing neutrophilic leucocytosis and anemia were seen in high- and intermediate-dose groups, particularly in females. Female animals also tended to develop enlarged adrenals, depressed glucose and elevated alkaline phosphatase levels.

Long term oral administration of 0 to 50 mg/kg/day diclofenac sodium to baboons also resulted in gastrointestinal ulceration. Constipation, with occasional episodes of diarrhea, was a marked feature. In all animals, there was a dose-related fall in serum albumin; anemia and an increased ESR were observed with the high dose. All physical and haematological parameters returned to normal values during subsequent recovery period.

Diclofenac sodium had no mutagenic effects and was not carcinogenic in rodent models.

**Local Irritation Studies**

1-Week Study in Rabbits
For 5 consecutive days, 0.1 mL diclofenac sodium solution (0.3% or 0.5%) or vehicle placebo was administered into the conjunctival sac of the rabbit eye. The left eye was treated, while the right served as control. Slit lamp evaluations, performed 6 and 24 hours after each instillation, revealed that both strengths of diclofenac sodium were virtually non-irritant.

2-Week Study in Rabbits
Solutions of 0.25% and 0.5% diclofenac sodium (50 u L) were instilled 8 times daily into the lower conjunctival sac of the rabbit eye. One group received a saline solution to act as the control. After 2 weeks of treatment, there were no signs of irritation or alterations in the ophthalmic structures or tissues of the eyelid. IOP in the treated eye and control groups was comparable.

4-Week Study in Rabbits
0.1% diclofenac sodium was instilled into the conjunctival sac 5 times per day for 4 consecutive weeks. Ophthalmic examinations, performed twice daily throughout the treatment period, remained normal. At the conclusion of treatment, there were no haematological or biochemical abnormalities and histopathological examinations failed to reveal any treatment-related systemic or macroscopic abnormalities.

3-Month Studies in Rabbits
Rabbits received 5 daily instillations of either a 0.1% or 0.05% diclofenac sodium ophthalmic solution in the conjunctival sac for 3 months. A third group received saline only. In each animal, the left eye was treated, allowing the right eye to act as a control.

Clinical examinations revealed no systemic or local abnormalities. Detailed ophthalmologic observations and laboratory and pathological examinations of the ophthalmic structures confirmed that diclofenac sodium 0.1% solution is safe when administered topically to the rabbit eye for protracted periods.
REFERENCES


2. Behrens-Baumann, W.: Inhibition of inflammation and prophylaxis of cystoid macular oedema following intracapsular cataract operation and lens implantation. Data-on File, Dispersa Inc., Mississauga, Ontario

3. Boles-Carenini, B.: Naclof7 (0.1% diclofenac sodium) ophthalmic solution in the treatment of patients undergoing cataract removal: a double-blind study versus 0.1% dexamethasone disodium phosphate. Internal Dispersa Report, March, 1988


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