

PRODUCT MONOGRAPH

Pr DICLOFENAC

Diclofenac Sodium Ophthalmic Solution,

0.1% w / v

Anti-inflammatory Analgesic Agent

Pharma Stulln Inc.

6500 TransCanada Highway, Suite 400
Pointe-Claire, Quebec
H9R 0A5

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Topical Ophthalmic	Ophthalmic Solution Diclofenac sodium 0.1% w/v	Non-medicinal ingredients: <i>Boric Acid, Trometamol, Macrogolglycerol Ricinoleate, Sodium Hydroxide, Purified Water</i> (No preservative)

INDICATIONS AND CLINICAL USE

DICLOFENAC (diclofenac sodium ophthalmic solution) 0.1% w/v 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 diclofenac sodium ophthalmic solution have not been established in children under 18 years of age. DICLOFENAC is not indicated for use in children.

Geriatrics (over 65 years of age):

Diclofenac sodium ophthalmic solution was well tolerated by elderly patients (see **WARNINGS AND PRECAUTIONS – Special Populations**).

CONTRAINDICATIONS

Known hypersensitivity to diclofenac sodium or to any ingredient in the formulation or any component of the medication. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

As with other non-steroidal anti-inflammatory agents, DICLOFENAC is contraindicated in patients in whom attacks of asthma, urticaria, acute rhinitis or other allergic manifestations are precipitated by acetylsalicylic acid or by other drugs with prostaglandin synthesis inhibiting activity. There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents.

WARNINGS AND PRECAUTIONS

General

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

The anti-inflammatory activity of ophthalmic diclofenac may mask the onset and/or progression of ocular infections; physicians should be alerted of 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 DICLOFENAC.

Hematologic

Patients receiving other medications which may prolong bleeding time, or with known hemostatic defects, may experience exacerbation with diclofenac sodium ophthalmic solution.

With some non-steroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied non-steroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery. Caution should be exercised when using NSAIDs postoperatively as well as in conjunction with agents that prolong bleeding time.

Ophthalmologic

Patients with evidence of corneal epithelial breakdown should immediately discontinue use of DICLOFENAC and should be monitored closely for corneal health.

All topical non-steroidal 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 DICLOFENAC, and topical steroids may increase the potential for healing problems. It should also be noted that concomitant use of DICLOFENAC 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 INTERACTIONS, 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. Topical NSAIDs, such as DICLOFENAC, 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 (IOP). A slight and transient elevation in IOP has been observed in some patients, following surgery, even with the use of DICLOFENAC.

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

Hepatic and Renal Impairment

The effect of hepatic impairment on diclofenac pharmacokinetics is not well understood; however, there were no detectable levels of drug in plasma, indicating that no measurable systemic absorption occurs following a single instillation of the ophthalmic drops.

Pregnant Women:

The safety of diclofenac sodium ophthalmic solution 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 diclofenac sodium ophthalmic solution 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):

Diclofenac sodium ophthalmic solution was well tolerated by patients presenting with posttraumatic 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 diclofenac sodium ophthalmic solution have not been established in children under 18 years of age. DICLOFENAC is not indicated for use in children.

Effects on ability to drive and use machines

Patients experiencing visual disturbances, in particular blurred vision, should refrain from driving a vehicle or operating machines.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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 dyspnea 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, diclofenac sodium ophthalmic solution 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 two 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 diclofenac sodium ophthalmic solution; 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 and rheumatoid arthritis, diclofenac has been associated with ulcerative keratitis, corneal thinning, punctate keratitis, corneal epithelial defect and corneal edema, which might become sight-threatening.

Allergic conditions have been reported such as conjunctival hyperemia, conjunctivitis allergic, erythema of eyelid, eye allergy, eye irritation, eye discharge, eyelid irritation eyelid edema, conjunctival edema, conjunctival follicles, eyelid pruritus, ocular hyperemia, urticaria, rash, eczema, erythema, pruritus, hypersensitivity, asthma, dyspnea, cough and rhinitis.

Other observed reactions include: ocular discomfort, impaired healing, corneal perforation, and eyelid margin crusting.

DRUG INTERACTIONS

Drug-Drug Interactions

Concomitant use of DICLOFENAC with topical corticosteroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications, such as slowed or delayed corneal healing; therefore caution should be exercised.

It should also be noted that concomitant use of DICLOFENAC with medications that prolong bleeding time may increase the risk of hemorrhage.

Ocular diclofenac at 0.1% has been used safely in clinical studies in combination with antibiotics for ocular use.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

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, diclofenac sodium ophthalmic solution has been combined with such standard pretreatment measures as mydriatics and topical antibiotics.

To reduce systemic absorption and increase local activity, nasolacrimal occlusion or eyelid closure is recommended for 2 minutes after instillation.

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.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 diclofenac sodium ophthalmic solution contains a total of only 5 mg diclofenac sodium, equivalent to just 3% of the normal recommended oral adult dose.

If DICLOFENAC is accidentally ingested, fluids should be taken to dilute the medication.

ACTION AND CLINICAL PHARMACOLOGY**Mechanism of Action**

Diclofenac sodium is a non-steroidal 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 diclofenac sodium ophthalmic solution has been found to inhibit miosis during cataract surgery, to reduce inflammation following surgical interventions, trauma, and in other non-infected inflammatory conditions. Diclofenac sodium ophthalmic solution 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 diclofenac sodium ophthalmic solution.

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:

DICLOFENAC (diclofenac Sodium ophthalmic solution) 0.1% w/v can be stored at room temperature between 15°C to 30°C. Protect from light.

Others:

“Keep out of the reach and sight of children”

SPECIAL HANDLING INSTRUCTIONS

Single use only.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DICLOFENAC (diclofenac sodium) 0.1% ophthalmic solution is a preservative-free, the eye drops are filled into unit dose containers of 0.3 mL each and as a, 10, 20 or 50 fold block then sealed in Al laminated sachets.

In addition to the active ingredient, diclofenac sodium, each mL also contains the non-medicinal ingredients: Boric Acid, Trometamol, Macrogolglycerol Ricinoleate, Sodium Hydroxide, and Purified Water.

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

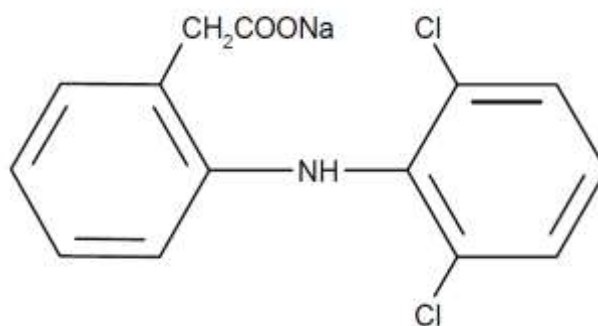
Drug Substance

Proper Name: Diclofenac Sodium

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

Molecular formula and molecular weight: $C_{14}H_{10}Cl_2NNaO_2$

Structural Formula:



Molecular weight: 318.1

Physicochemical properties:

Description: Diclofenac sodium active ingredient is white or slightly yellowish crystalline powder, slightly hygroscopic practically odorless

Solubility: At 25°C Diclofenac Sodium is slightly soluble in acetone, sparingly soluble in water, Soluble in alcohol, freely soluble in methanol and practically insoluble in ether and chloroform.

CLINICAL TRIALS

Diclofenac sodium ophthalmic solution 0.1% w/v 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 diclofenac sodium ophthalmic solution 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 diclofenac sodium ophthalmic solution 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 diclofenac sodium ophthalmic solution treatment.

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

Diclofenac sodium ophthalmic solution was effective in reducing or eliminating such post-operative inflammatory responses as anterior chamber turbidity, corneal edema, elevated protein levels, ciliary injection and conjunctival hyperemia. In addition, post-operative pain was consistently reduced. Diclofenac sodium ophthalmic solution 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.

Diclofenac sodium ophthalmic solution was well tolerated by patients presenting with posttraumatic 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 diclofenac sodium ophthalmic solution, 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).

Preparation	Inhibition of Edema Induced by	
	Carrageenin (ED ₅₀ mg/kg) p.o.*	Kaolin (ED ₅₀ mg/kg) p.o.*
Diclofenac sodium	2.1	1.2

* 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 non-steroidal anti-inflammatory agents, including the standard, indomethacin.

Irritant	% Inhibition	
	0.1% diclofenac	0.1% indomethacin
Carrageenin	31.9%	Not available
Yeast	29.2%	21.2%
Albumin	24.4%	22.0%
Mustard	20.7%	19.6%

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 (3×10^{-6} to 3×10^{-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 $72 \pm 7\%$ which compared very favourably to indomethacin and was superior to other non-steroidal 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 mcL 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 $\geq 0.064\%$, 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 mcL 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 mcL 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 mcL 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.

Effects of diclofenac 0.25% and indomethacin 0.5% eye drops on uveitis induced by bovine serum albumin in rabbits

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

+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 was 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 deepithelialization. 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 mcg/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 μM/L) was 1.6.

Platelet Adhesiveness

At 15 mcg/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 mcL application of 50 mcg 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 mcg per eye

Tissue*	Time Interval			
	0.5 hour	1.0 hour	3.0 hour	6.0 hour
Blood	0.053	0.015	0.009	0.010
Cornea	8.366	3.451	1.120	2.126
Conjunctiva	4.722	0.933	0.428	0.600
Nictitating Mem.	2.814	0.461	0.460	0.196
Ciliary body	0.564	0.211	0.067	0.161
Sclera	0.470	0.105	0.60	0.086
Choroid/retina	0.451	0.099	0.041	0.040
Iris	0.358	0.228	0.116	0.275
Aqueous humour	**	0.168	0.050	**
Optic nerve	0.071	0.076	0.076	**
Vitreous humour	0.025	0.007	**	**
Lens	0.014	0.008	0.006	0.012

*Concentrations expressed as mcg/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:

Species	Volume Diclofenac-Na (mL/kg)	Dose Equivalent (mg/kg)	Mortality
Mice (Males and Females)	5	5	0/10
	30	30	0/10
	50	50	7/10
	100	30	3/15
Rats (Males and Females)	30	30	0/10
	50	50	1/10

The oral LD₅₀ 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 LD₅₀ 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. Hematologic 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 hematological 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 mcL) 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 hematological 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.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr DICLOFENAC

Diclofenac Sodium Ophthalmic Solution, 0.1% w / v

This leaflet is part III of a three-part “Product Monograph” published when DICLOFENAC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DICLOFENAC. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Your doctor has prescribed DICLOFENAC (diclofenac sodium) solution, 0.1% w/v for you which is a non-steroidal anti-inflammatory drug (NSAID), used to treat eye inflammation after cataract surgery and eye inflammation after a non-penetrating eye injury.

What it does:

DICLOFENAC eye drops reduce pain and inflammation by reducing the production of certain substances called prostaglandins.

When it should not be used:

DO NOT USE DICLOFENAC eye drops if you are allergic to diclofenac sodium, any other ingredient in the formulation (see **What the non-medicinal ingredients are**), or other medications of the NSAID group, such as acetylsalicylic acid, diflunisal, ibuprofen, flurbiprofen, ketoprofen, indomethacin, mefenamic acid, piroxicam, sulindac, or tiaprofenic acid.

DICLOFENAC is not for use in children under 18 years of age.

What the medicinal ingredient is:

Diclofenac sodium, 0.1% w/v

What the non-medicinal ingredients are:

Boric Acid, Trometamol, Macrogolglycerol Ricinoleate, Sodium Hydroxide, Purified Water.

What dosage forms it comes in:

0.1% (diclofenac sodium) w/v ophthalmic solution is available in plastic unit dose container of 0.3 mL.

WARNINGS AND PRECAUTIONS

BEFORE taking DICLOFENAC, tell your doctor or pharmacist if you:

- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding or planning to breastfeed;
- are taking a topical corticosteroid. Taking DICLOFENAC and a corticosteroid at the same time may slow wound healing;
- have (had) complicated eye surgery, pre-existing corneal problems, diabetes, problems with your eye surface (such as dry eye), rheumatoid arthritis or multiple eye surgeries. You may be a higher risk for developing serious eye side effects.
- Taking DICLOFENAC more than 24 hours before eye surgery or for more than 14 days after surgery may also increase your risk for developing serious eye side effects;
- have any other medical problem(s);
- wear soft contact lenses. DO NOT administer DICLOFENAC while wearing soft contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.

WHILE taking DICLOFENAC:

- check with your doctor if you are not getting any relief or if any problems develop, such as an eye infection or bleeding problems;
- report any reactions to your doctor. This is very important because it will help in the early detection and prevention of problems;
- If you experience any vision problems, in particular blurring of vision, DO NOT drive or operate any machinery.

STOP using DICLOFENAC and talk to your doctor if you experience any serious problems with your eye(s).

Your regular medical check-ups, including monitoring of eye pressure, are essential.

INTERACTIONS WITH THIS MEDICATION

BEFORE taking DICLOFENAC, tell your doctor or pharmacist if you are taking any other drug (either prescription or non-prescription) such as:

- corticosteroids
- medications that prolong bleeding time

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- antibiotics

PROPER USE OF THIS MEDICATION

DICLOFENAC is for topical use only.

Usual adult dose:

Cataract surgery

Before surgery: Apply 1 drop into the affected eye(s) up to 5 times during the 3 hours before your scheduled surgery.

After surgery: Apply 1 drop into the affected eye(s) 15, 30 and 45 minutes following surgery. Then apply 1 drop 3 to 5 times per day for up to 4 weeks.

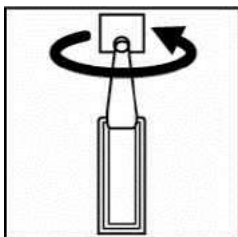
Inflammation from non-penetrating wounds Apply 1 drop into the affected eye(s) 4 to 5 times per day as directed by your physician.

How to use this medication:

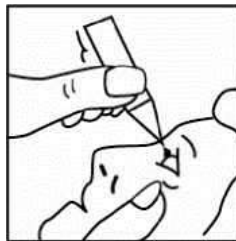
Open the drops container just before you want to use it. After using the drops, throw away what is left. This is because the drops cannot be kept free of bacteria after being opened.



1. First wash your hands and then break off a single dose container from the strip. Then twist open the top of the single dose container as shown. Each single dose container contains enough solution for both eyes. If you wear contact lenses, remove them before using your eye drops.



2. Pull down your lower eyelid with a clean finger until there is a 'pocket' between the eyelid and your eye. This is where the drop will go. Bring the single dose container close to the eye. Do this in front of the mirror if it helps.



3. Close your eyelid and gently press the inner corner of your eye with your forefinger for 2 minutes.



4. Wipe any excess liquid from your face with a tissue. If you must use more than 1 drop in the same eye, wait at least 5 minutes before applying the next drop. Eye ointments should be applied last.

5. Wash your hands to remove any medication. Discard unused portion.

Overdose:

If you think you have taken too much DICLOFENAC, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdosage will not usually cause sudden problems. If DICLOFENAC is accidentally ingested, fluids should be taken to dilute the medication.

Missed Dose:

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. DO NOT double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Occasionally you may experience a mild to moderate burning sensation when DICLOFENAC is instilled in the eye. This symptom usually disappears rapidly, but

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if it or any other side effects persist, check with your doctor.

Less frequently observed eye side effects are allergic reaction, itchy eye(s), reddening of eye and blurred vision immediately after instillation of the eye drops, eye pain, eye surface inflammation with surface damage, sensitivity to light, abnormal vision, eye allergy, eye swelling, clouding of the eye surface, eyelid swelling, eye irritation, eye discharge, eyelid reddening, swelling or rash, eye crusting, eye discomfort, slower healing and a stainable cornea.

Uncommon side effects in the rest of the body are bad taste, feeling of pressure, abdominal pain, feeling weak, chills, dizziness, swelling of the face, fever, headache, problems sleeping, nausea, pain, nose irritation, a viral infection, hives, rash, eczema, skin redness, cough, allergic reaction and vomiting.

If you are using DICLOFENAC after cataract surgery, you may feel increased eye pressure (intraocular pressure).

If you are using DICLOFENAC after refractive surgery, you may notice tearing.

If you use corticosteroids, have infections or have rheumatoid arthritis, you may develop ulcers, thinning or inflammation of your cornea, which may cause loss of vision.

Report any reactions to your doctor. This is very important because it will help in the early detection and prevention of problems.

What Diclofenac UD looks like and contents of the pack

Unit dose containers made of LDPE with:
 10 x 0.3 ml
 20 x 0.3 ml
 50 x 0.3 ml

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	Ulcer, thinning or swelling of your cornea		<input checked="" type="checkbox"/>	
	Outer layer defects of your cornea		<input checked="" type="checkbox"/>	
	Shortness of breath			<input checked="" type="checkbox"/>
	Increase in signs and symptoms of asthma		<input checked="" type="checkbox"/>	
	Severe allergic reaction			<input checked="" type="checkbox"/>
	Tiny tears (perforations)		<input checked="" type="checkbox"/>	
Unknown	In your cornea		<input checked="" type="checkbox"/>	

This is not a complete list of side effects. For any unexpected effects while taking DICLOFENAC, contact your doctor or pharmacist.

HOW TO STORE IT

Store the unique dose container at room temperature between 15° and 30 °C. Protect from light.

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting

<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>

for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects.

The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be found in the Health Canada website or by contacting.

Pharma Stulln Inc.

6500 TransCanada Highway, Suite 400
Pointe Claire, Quebec
H9R 0A5

E-mail: info@pharmastulln.ca

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