PRODUCT MONOGRAPH

Pr VOLTAREN* OPHTHA

Diclofenac Sodium Ophthalmic Solution

0.1% w/v

Anti-inflammatory Analgesic Agent

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec
H9S 1A9

www.novartis.ca

Date of Revision:
May 31, 2017

Submission Control No.: 204978

Table of Contents

[Pr]VOLTAREN* OPHTHA

Diclofenac Sodium Ophthalmic Solution

0.1% w/v

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical Ophthalmic	Ophthalmic solution diclofenac sodium 0.1% w/v	Sorbic Acid 0.2% (Preservative) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

VOLTAREN*OPHTHA (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 VOLTAREN* OPHTHA have not been established in children under 18 years of age. VOLTAREN* OPHTHA is not indicated for use in children.

Geriatrics (over 65 years of age):
VOLTAREN* OPHTHA 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, VOLTAREN* OPHTHA 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 acetylsalicy1ic 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 VOLTAREN* OPHTHA.

Hematologic

Patients receiving other medications which may prolong bleeding time, or with known hemostatic defects, may experience exacerbation with VOLTAREN* OPHTHA**.**

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 VOLTAREN* OPHTHA 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 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 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 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 (IOP). A slight and transient elevation in 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

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 VOLTAREN* OPHTHA 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 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.

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, 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 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 VOLTAREN* OPHTHA (diclofenac sodium ophthalmic solution), 0.1% w/v 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 VOLTAREN* OPHTHA 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, VOLTAREN* OPHTHA has been combined with such standard pre-treatment 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

There has been limited experience with diclofenac sodium overdosage, 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 in bottles should be stored at 20 to 25^{o}C with excursions permitted to 15^{o} to 30^{o} C. Protect from light.

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VOLTAREN* OPHTHA is available in dropper bottles of 5 mL and twin pack containing 2 bottles of 5 mL per box preserved with sorbic acid.
Composition:

- Active ingredient: Diclofenac sodium
- Non-Medical ingredients:
  Boric acid,
  Edetate Disodium,
  Cremophor EL,
  Purified water,
  Sorbic Acid,
  Tromethamine (TRIS)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

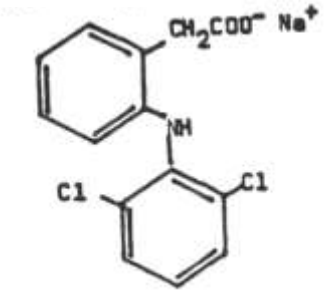
Brand name: VOLTAREN* OPHTHA (diclofenac sodium ophthalmic solution), 0.1% w/v

Proper name: Diclofenac sodium

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

Molecular formula and molecular mass: $C_{14}H_{10}Cl_2NO_2Na$, 318.1

Structural formula:



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 (diclofenac sodium) 0.1% w/v ophthalmic solution 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).

	Inhibition of edema induced by	
Preparation	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 nonsteroidal 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 ± 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 *u*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 *u* 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* l 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* l 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 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 E_2 formation, which parallels antipyresis, but does not induce hypothermia in the afebrile animal. The inhibition of prostaglandin synthesis *in vitro* (IC_{50} *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 ^{14}C-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 *u*g 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 *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:

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

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. 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 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

1. Agata, M., Mizuno, Y. and Abe, T.: Effects of nonsteroidal anti-inflammatory agent, diclofenac sodium eye drops, on experimentally caused conjunctivitis of rats. Fol. Ophth. Jap. 35: 604-612, 1984

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.: Naclof® (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

4. Bonomi, L., Perfetti, S. and Bellucci, R.: Prevention of surgically-induced miosis by diclofenac eye drops. Ann. Ophthal. 19: 142-145, 1987

5. Brogdan, R.N., Heel, R.C., Pakes, G.E. et al: Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. Drugs 20: 24-48, 1980

6. Congdon NG, Schein OD, von Kulajta P, Lubomski LH, Gilbert D, Katz J. Corneal complications associated with topical ophthalmic use of nonsteroidal anti-inflammatory drugs. J Cataract Refract Surg 2001 Apr;27(4):622-31.

7. Dadeya S, Kamlesh (2002) Comparative evaluation of diclofenac and dexamethasone following strabismus surgery. J Pediatr Ophthalmol Strabismus; 39(3):166-8.

8. Gabison EE, Chastang P, Menashi S, et al (2002) Corneal perforation following photorefractive keratectomy and prolonged use of diclofenac; ARVO-abstracts; May 02.

9. Guidera AC, Luchs JI, Udell IJ. Keratitis ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. Ophthalmology 2001 May;108(5):936-44.

10. Hayashi, M., Araie, M. and Motonari, M.: The effects of diclofenac eye drops on inflammation following cataract surgery. Ganka Rinsho Iho. (J) 78. 4, 1984

11. Ilic, J. et al: Comparison de l'effet anti-inflammatoire des collyres de dexamethasone et de diclofenac. Klin. Mbl. Augenheilk. 186: 494-498, 1984

12. Kobayashi, C. et al: The efficacy of the nonsteroidal anti-inflammatory preparation diclofenac sodium aqueous eye drops on postoperative inflammation. Ganka Rinsho Iho.. (J) 78: 3, 1984

13. Krupp, P. et al: (The mechanism of the effect of Voltaren). Therapiewoche 26: 3-20, 1976

14. Kulkarni, P. and Srinivasan, B.C.: Diclofenac and enolicam as ocular anti-inflammatory drugs in rabbit corneal wound model. J. Ocular Pharmacol. 2: 171-175, 1986

15. Laitinen J, Nuutinnen LS, Puranen J, Ranta P, Salomaki T, Effect of non-steroidal anti-inflammatory drug, diclofenac, on haemostasis in patients undergoing total hip replacement. Acta Anaesthesiol Scand 1992: 36: 486-489.

16. Leuenberger, P.: Open study of diclofenac eye drops in the treatment of various ocular diseases. Data-on-file, CIBA Vision, Mississauga, Ontario

17. Lin JC, Rapuano CJ, Laibson PR, Eagle RC Jr, Cohen EJ. Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. Arch Ophthalmol 2000 Aug;118(8):1129-32.

18. Masuda, K. et al: The efficacy of diclofenac sodium eye drops in postoperative inflammation. Ganka Rinsho Iho.. (J) 80: 1545-1563, 1986

19. Menassé, R., Hedwell, P.R., Kraetz, J. et al: Pharmacological properties of diclofenac sodium and its metabolites. Scand. J. Rheumatol.22 (Suppl.): 5-15, 1978

20. Merté, H.J.: Inhibition of operative miosis by diclofenac eye drops. Internal Dispersa Report, May 20, 1985

21. Pharmakakis NM, Andrikopoulos GK, Papadopoulos GE, et al (2002) Does identification of the causal organism of corneal ulcers influence the outcome. Eur.J.Ophthalmol; 13(1):11-7.

22. Riess, W. and Stierlin, H.: Pharmacokinetics and metabolism of the anti-inflammatory agent, Voltaren. Scand. J. Rheumatol. 22 (Suppl.): 17-29, 1978.

23. Robertson S. Alcon recalls its generic diclofenac. Ocular Surgery News 1999;17/21:1.

24. Ronen, S., Rozeman, Y., Zylbermann, R. et al: Treatment of ocular inflammation with diclofenac sodium double-blind trial following cataract surgery. Ann. Ophthal. 177: 577-581, 1985

25. Rossetti L, Bujtar E, Castoldi D, et al (1996) Effectiveness of diclofenac eyedrops in reducing inflammation and the incidence of cystoic macular edema after cataract surgery. J Cataract Surg; 22 (Suppl 1):794-9.

26. Rowland, J.M., Ford, C.J., Della Puca, R.A. et al: Effects of topical diclofenac sodium in a rabbit model of ocular inflammation and leukotaxis. J. Ocular Pharmacol. 2: 23-29, 1986

27. Stodmeister, R. and Marquardt, R.: A nonsteroidal anti-inflammatory agent in chronic conjunctivitis. A double-blind study of Naclof and dexamethasone. Fortschr. Ophthalmol. 83: 199-202, 1986

28. Todd, P.A. and Sorkin, E.M.: Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. Drugs 35: 244-285, 1988

29. Van Haeringen, N.J., Oosterhuis, J.A., Van Delft, J.L. et al: Drug prevention of blood-aqueous barrier disruption. Ophthalmic Res. 15: 180-184, 1983

30. Van Husen, H.: Topical treatment of anterior ocular diseases with diclofenac Na eye drops. Klin. Mbl. Augenheilk. 188: 615-619, 1986

31. Witmer, R. and Zinkernagel, R.: Double-blind randomized trial of diclofenac eye solution versus prednisolone eye solution on preoperative prophylaxis and postoperative treatment of inflammation in patients undergoing intraocular lens extraction and implantation. Data-on-file, CIBA Vision, Mississauga, Ontario

PART III: CONSUMER INFORMATION

Pr VOLTAREN* OPHTHA
(Diclofenac Sodium Ophthalmic Solution)

0.1% w/v

This leaflet is part III of a three-part "Product Monograph" published when VOLTAREN* OPHTHA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VOLTAREN* OPHTHA. 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 VOLTAREN* OPHTHA (Diclofenac Sodium ophthalmic solution), 0.1% w/v for you which is a nonsteroidal anti-inflammatory drug (NSAID), used to treat eye inflammation after cataract surgery and eye inflammation after a non-penetrating eye injury.

What it does:
VOLTAREN* OPHTHA eye drops reduce pain and inflammation by reducing the production of certain substances called prostaglandins.

When it should not be used:
DO NOT USE VOLTAREN* OPHTHA if you are allergic to diclofenac sodium, any other ingredient in the formulation (see **What the nonmedicinal 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.

VOLTAREN* OPHTHA is not for use in children under 18 years of age.

What the medicinal ingredient is:
Diclofenac sodium, 0.1% w/v

What the nonmedicinal ingredients are:
Boric acid,
Edetate Disodium,
Cremophor EL,
Tromethamine (TRIS),
Sorbic Acid.
Water

What dosage forms it comes in:
VOLTAREN* OPHTHA is available in:
Preserved multi-dose bottles of 5mL and twin pack containing 2 bottles of 5 mL per box.

WARNINGS AND PRECAUTIONS

BEFORE taking VOLTAREN* OPHTHA, tell your doctor or pharmacist if you:

- are pregnant or are planning to become pregnant while taking this medication;
- are breastfeeding or planning to breastfeed;
- are taking a topical corticosteroid. Taking VOLTAREN* OPHTHA 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 VOLTAREN* OPHTHA 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 VOLTAREN* OPHTHA while wearing soft contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.

WHILE taking VOLTAREN* OPHTHA:

- 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 VOLTAREN* OPHTHA 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 VOLTAREN* OPHTHA, 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
- antibiotics

PROPER USE OF THIS MEDICATION

VOLTAREN* OPHTHA is for topical use only.

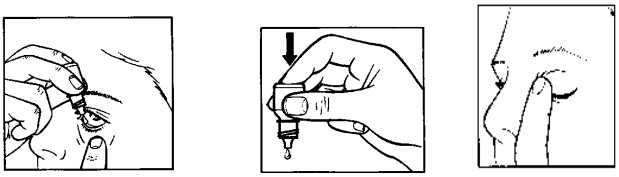
Usual adult dose:

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:



1 2 3

- Wash your hands and sit or stand comfortably. If you wear contact lenses, remove them before using your eye drops.
- Visually inspect the dropper tip to make sure that it is not chipped or cracked.
- Avoid touching the dropper tip against your eye or anything else to avoid contamination. Eye drops and eye dropper must be kept clean.
- Pull down your lower eyelid with a clean finger until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Gently press on the base of the bottle to release one drop of VOLTAREN* OPHTHA at a time.
- DO NOT squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).
- Close your eyelid and gently press the inner corner of your eye with your forefinger for 2 minutes (picture 3).
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use. DO NOT wipe or rinse the dropper tip.
- If a drop misses your eye, try again.
- Wipe any excess liquid from your face with a tissue.
- If you are to use more than one drop in the same eye, wait at least 5 minutes before applying the next drop. Eye ointments should be applied last.
- Wash your hands to remove any medication.

Overdose:

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

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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 VOLTAREN* OPHTHA is instilled in the eye. This symptom usually disappears rapidly, but 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, eyelid 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 VOLTAREN* OPHTHA after cataract surgery, you may feel increased eye pressure (intraocular pressure).

If you are using VOLTAREN* OPHTHA 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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Uncommon	**Ulcer, thinning or swelling of your cornea**		√	
	Outer layer defects of your cornea		√	
	Shortness of breath			√
	Increase in signs and symptoms of asthma		√	
	Severe allergic reaction			√
Unknown	**Tiny tears (perforations) in your cornea**		√	

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

HOW TO STORE IT

Store at 20°C to 25°C with excursions permitted to 15°C to 30°C. Protect from light.

Keep bottle tightly closed when not in use. Keep this and all medication in a safe place out of the reach and sight of children.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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

This document plus the full product monograph, prepared for health professionals can be found on the Health Canada website or by contacting the sponsor,

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec
H9S 1A9
at 1-800-363-8883 or at www.novartis.ca

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last revised: May 31, 2017

*a trademark of Novartis