PRODUCT MONOGRAPH

INDOCID® OPHTHALMIC SUSPENSION

(indomethacin ophthalmic suspension)

ANTI-INFLAMMATORY

MERCK SHARP & DOHME CANADA
DIVISION OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC, CANADA

Date of Revision:
JULY 7,1988

2HN820027B

ACTIONS

INDOCID® OPHTHALMIC SUSPENSION 1% (indomethacin ophthalmic suspension) is a 1% suspension of indomethacin for use in the eye.

Indomethacin appears to stabilize the blood-aqueous barrier. In a series of patients undergoing extracapsular cataract extraction with implantation of an intraocular lens who were treated with 4 drops daily of indomethacin ophthalmic suspension and evaluated by fluorescein dye technique, there were significantly smaller increases in fluorescein concentration in the anterior chamber relative to the unoperated eye, than in patients on placebo. The median increases (from pre-treatment) in fluorescein concentration 0-6 days and 1-3 weeks post surgery were, respectively, 16% for indomethacin ophtalmic suspension and 72% for placebo ($p<0.01$), and 18% for indomethacin ophthalmic suspension 1% and 84% for placebo ($p<0.01$).

In studies, in which patients underwent extracapsular cataract extraction with implantation of a posterior chamber intraocular lens, indomethacin ophthalmic suspension reduced the incidence of angiographically-documented aphakic cystoid macular edema, and more patients without aphakic cystoid macular edema obtained visual acuity of 20/30 or better compared to those patients with aphakic cystoid macular edema.

The results of double-masked, placebo-controlled studies measuring pupil diameter demonstrate that the administration of INDOCID® OPHTHALMIC SUSPENSION 1% in the operative eye four times-a-day on the day prior to cataract surgery, and one drop 45 minutes before surgery is usefull for maintaining mydriasis during cataract extraction.

Pharmacokinetics

Mean aqueous humor levels of indomethacin in two groups of patients receiving either one drop of indomethacin ophthalmic suspension 1% for five doses spaced over 24 hours, or one drop every ten minutes for five doses 18 hours before surgery followed by one drop each at 12 hours, 6-10 hours, 2 hours, 90 minutes, and 30 minutes before surgery were 204 ng/mL for patients in the first indomethacin group and 252 ng/mL for patients in the second indomethacin group.

Serum levels were assayed from 30 patients; 15 patients were sampled from each of the two different regimens of indomethacin 1% treatments. There were no detectable serum levels of indomethacin with either regimen.

INDICATIONS AND USAGE

INDOCID® OPHTHALMIC SUSPENSION 1% (indomethacin ophthalmic suspension) is indicated for the prophylaxis of cystoid macular edema following cataract surgery.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

PRECAUTIONS

General

Systemically-administered non-steroidal anti-inflammatory drugs should not be used in patients who have previously exhibited bronchospastic reactions to acetylsalicylic acid or to this class of drugs. The response of this small group of patients to topical administration of indomethacin is unknown.

The effect of topical indomethacin in the presence of eye infections has not been studies.

Pregnancy

There are no adequate or well-controlled studies in pregnant women. INDOCID® OPHTHALMIC SUSPENSION 1% (indomethacin ophthalmic suspension) should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether indomethacin is excreted in human milk following ocular administration. Because systemically-administered indomethacin is excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The adverse reactions reported in clinical studies are listed as follows in an approximate decreasing order of occurrence:

Redness of the eye
Burning upon instillation
Elevated intraocular pressure
Eyelid edema
Corneal epithelial defects (e.g. corneal abrasion, punctate keratitis)
Eye discomfort (pain, irritation)
Itching
Corneal edema and striate keratopathy

DOSAGE AND ADMINISTRATION

Shake container before administration of the product.

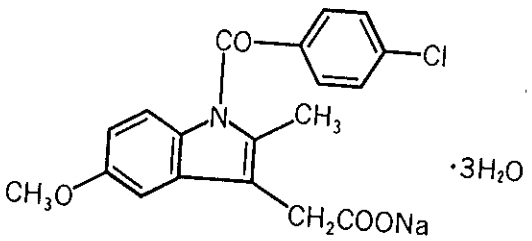
Instill one drop of INDOCID® OPHTHALMIC SUSPENSION 1% (indomethacin ophthalmic suspension) in the operative eye four times a day on the day prior to surgery, and one drop 45 minutes before surgery. Continue to instill 1 drop in the eye four times daily for approximately 10-12 weeks after surgery.

AVAILABILITY

Ca 9635 - INDOCID® OPHTHALMIC SUSPENSION 1% (indomethacin ophthalmic suspension), a sterile, white, flocculated suspension containing 10 mg indomethacin in each milliliter, (1.0%), is supplied in a 5 mL dropper bottle.

CHEMISTRY

Indomethacin,
1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, is a yellowish-white powder insoluble in water but soluble in alcohols, having the following structural formula.



Molecular Formula: $C_{19}H_{16}ClNO_4$

Molecular Weight: 357.80

PHARMACOLOGY

Indomethacin is a potent inhibitor or prostaglandin synthetase. Indomethacin ophthalmic suspension has been demonstrated to inhibit production of prostaglandins in the eye in several animal models.

In the eye, in animal studies, prostaglandins have been shown to produce disruption of the blood/aqueous barrier, vasodilatation, increased vascular permeability, leucocytosis, increased intraocular pressure and miosis.

Elevated levels of prostaglandins have been found in the eyes of rabbits and other species following experimentally-induced trauma. Since indomethacin is an inhibitor of prostaglandin synthetase, its mode of action may be due to a decrease of prostaglandin synthesis in the eye.

In rabbits, suspension of 1% indomethacin has been shown to penetrate the cornea rapidly and to prevent an increase in intraocular pressure induced by the administration of arachidonic acid.

ANIMAL TOXICOLOGY

Orally-administered indomethacin has been given to nine species of animals in short and long term studies. However, with the exception of pigs and chickens, the human dose is not tolerated. The main toxics signs exhibited are inflammation and/or ulceration of the gastrointestinal mucosa and diarrhea.

Reproduction and teratogenic studies have not been performed with indomethacin ophthalmic suspension. However in mice, rats and rabbits systemically-administered indomethacin showed no effect on fetal development or the reproduction cycle. There was some decrease in fetal viability and some delay in the onset of parturition in the rat, as has been observed with other non-steroidal anti-inflammatory agents. A similar delay in the onset of parturition was not observed in the rabit. Studies in mice demonstrated that indomethacin crosses the placental barrier.

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