NON-TERATOGENIC EFFECTS : Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular (closure of the ductus arteriosus), the use of **Amplinak™** during late pregnancy should be avoided.

NURSING MOTHERS : Amplinak™ is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Amplinak™** ophthalmic suspension is administered to a nursing woman.

PEDIATRIC USE : The safety and effectiveness of **Amplinak™** in pediatric patients below the age of 10 years have not been established.

GERIATRIC USE : No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS :

Ocular Adverse Reactions: The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These reactions occurred in approximately 5 to 10% of patients. Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% including conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these reactions may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions : Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

Instructions to patients : 1. **Amplinak™** should not be administered while wearing contact lens. 2. Do not touch the nozzle tip to any surface, as this may contaminate the solution. 3. Keep the bottle tightly closed when not in use. 4. Keep out of reach of children. 5. Use the suspension within one month of opening of container.

Dosage and Administration : One drop of **Amplinak™** ophthalmic suspension should be applied to the affected eye three-times-daily beginning 1 day prior to cataract surgery, continue on the day of surgery and through the first 2 weeks of the postoperative period.

HOW SUPPLIED :

Amplinak™ Ophthalmic suspension is supplied in 5 mL dropper bottles.

NOTE :

Store **Amplinak™** Ophthalmic suspension below **30°C.** Protect from sunlight.

Marketed by :
ALLERGAN INDIA PRIVATE LIMITED

Manufactured in India by :
Piramal Enterprises Limited
Plot No. 67-70, Sector 2, Pithampur-454 775,
Dist. Dhar, Madhya Pradesh

Updated on Nov 2016

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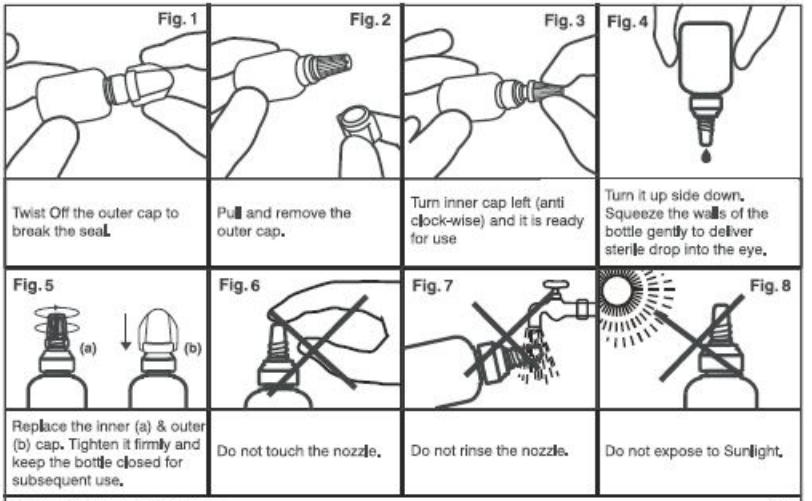


For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

NEPAFENAC OPHTHALMIC SUSPENSION 1mg/mL FOR TOPICAL OPHTHALMIC USE

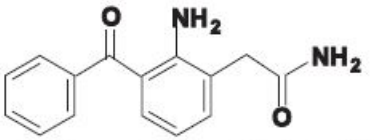
Amplinak™

ALLERGAN

DESCRIPTION :

Amplinak™

(Nepafenac ophthalmic suspension) 1 mg/mL, w/v is sterile, topical, nonsteroidal anti-inflammatory (NSAID) prodrug for ophthalmic use. Chemically nepafenac is 2-amino-3-benzoylbenzeneacetamide with an empirical formula of $C_{15}H_{14}N_2O_2$. the structural formula of nepafenac is:



Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28. **Amplinak™** ophthalmic suspension is supplied as a sterile, aqueous 0.1% suspension with a pH approximately of 7.4. The osmolality of **Amplinak™** ophthalmic suspension is approximately 305 mOsmol/kg.

COMPOSITION : Each mL of **Amplinak™** contains

Nepafenac	0.1% w/v
Stabilized Oxychloro Complex (As preservative)	0.01% w/v

INDICATIONS AND USAGE : Amplinak™ ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

CLINICAL PHARMACOLOGY :

PHARMACODYNAMICS : After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac is thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

PHARMACOKINETICS : Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours postdose, respectively, following bilateral topical ocular three - times - daily dosing of nepafenac ophthalmic suspension 0.1%.The mean steady - state Cmax for nepafenac and for amfenac were 0.310 $\pm$ 0.104 mg/ml and 0.422 $\pm$ 0.121 mg/ml, respectively, following ocular administration.

Nepafenac at concentration up to 300 mg/ml did not inhibit *in vitro* metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely. Drug - drug interactions mediated by protein are also unlikely.

CLINICAL STUDIES :

In two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period. **Amplinak™** ophthalmic suspension demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation. Patients treated with **Amplinak™** ophthalmic suspension were less likely to have ocular pain and measurable signs of inflammation (cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle.

For ocular pain in both studies a significantly higher percentage of patients (approximately 80%) in the nepafenac group reported no ocular pain on the day following cataract surgery (Day 1) compared to those in the vehicle group (approximately 50%).

Results from clinical studies indicated that **Amplinak™** has no significant effect upon intra-ocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

NON-CLINICAL TOXICOLOGY

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY : Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed in *vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay.

Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes in vivo in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg (approximately 90 and 380 times the plasma exposure to the parent drug, nepafenac, and the active metabolite, amfenac, respectively, at the recommended human topical ophthalmic dose)

CONTRAINDICATIONS : Amplinak™ is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAID

WARNINGS : For TOPICAL OPHTHALMIC USE ONLY NOT FOR INJECTION.

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives and other nonsteroidal anti - inflammatory agents. Therefore caution should be taken when treating individuals who have previously exhibited sensitivities to these drugs. With some nonsteroidal anti-inflammatory drugs including **Amplinak™**, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation, There have been reports that ocularly applied nonsteroidal anti - inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS : Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including **Amplinak™** may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including **Amplinak™** and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (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 which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events. It is recommended that **Amplinak™** ophthalmic suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

PREGNANCY : TERATOGENIC EFFECTS. Pregnancy Category C. Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 260 and 2400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses $\geq$ 10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well - controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, **Amplinak™** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.