2313

愛克樂®眼藥水 0.5%w/v
ACULAR® Ophthalmic Solution 0.5%w/v
(ketorolac tromethamine)

衛署藥輸字第 **022653** 號

性狀：

本品 1 ml 含有：活性成分 ketorolac tromethamine 5mg；保存劑 benzalkonium chloride 0.01%；非活性成分：edetate disodium 0.1%，octoxynol 40，氯化鈉，及純水。

動物藥理學：

Ketorolac tromethamine 可防止兔局部施用花生四烯酸出現眼內壓升高，於試管試驗中不會抑制兔水晶體之醛糖還原酵素。

本品不會促成 *Candida albicans, herpes simplex* 病毒一型或 *Pseudomonas aeruginosa* 於兔誘發眼部感染的傳播。

臨床藥理學：

本品乃非類固醇消炎藥，全身性投藥時具有止痛、消炎及解熱活性，其作用機轉相信部分係來自於其可抑制前列腺素(prostaglandin)之生物合成。眼部投予本品可降低眼水之前列腺素 E_2(PGE)濃度，接受媒劑之眼球之眼水中平均 PGE_2 濃度為 80 pg/ml，而接受愛克樂®0.5%眼藥水之眼球為 28 pg/ml。

Ketorolac tromethamine 於全身性投藥時不會造成瞳孔收縮。

臨床研究結果指出，本品對眼內壓不會造成顯著影響。

兩次對照臨床研究顯示本品用於緩解因季節性過敏性結膜炎引發的眼部搔癢，顯然比媒劑更有效。

兩次對照臨床研究顯示使用愛克樂®眼藥水治療兩週的病人，比使用媒劑處理病人，更少有可測量之發炎徵象(細胞及發紅)。兩滴(0.1 ml)愛克樂®眼藥水 0.5%於摘除白內障前 12 小時及 1 小時滴入病人眼部，9 位病人眼部中有 8 位達到可測量的程度(平均 ketorolac 濃度 95 ng/ml 眼水，40 至 170 ng/ml 範圍)，

一滴(0.05 ml)愛克樂®眼藥水 0.5%滴入 26位正常個體之一眼，而點一滴媒劑於另一眼，每日三次，於局部眼部治療期間於第 10 日，26 人中僅有 5 人血漿含有可檢測量之 ketorolac(10.7 至 22.5 ng/ml 之範圍)；當 ketorolac tromethamine 10 mg 每 6 小時全身性投藥時，穩定狀態的峰值血漿濃度約為 960 ng/ml。

本品可與其它眼科用藥併用而無安全上的考量，例如抗生素，貝它遮斷劑(β-blockers)，碳酸脫水酵素抑制劑，睫狀肌麻痺劑及散瞳劑。

適應症：

暫時緩解由於季節性過敏性結膜炎引發之眼部搔癢，白內障手術後之眼部發炎。

禁忌症：

禁忌用於對配方中之任一種成分過敏病人。

警語：

與乙醯基水楊酸(acetylsalicylic acid)，苯基乙酸衍生物(phenylacetic acid derivatives)及其它非類固醇抗炎劑可能產生交叉過敏，因此用於治療過去對此等藥物過敏病人時須特別審慎。某些非類固醇消炎藥由於干擾血小板凝結而可能延長出血時間，曾有報告於眼科手術時，眼部施用非類固醇抗炎藥引起眼部組織出血(包括眼前房出血)。

注意事項：

一般方面：推薦本品用於已知有出血傾向或接受其它可能延長出血時間藥物病人時應審慎。配戴隱形眼鏡時不可投予本品。

致癌性、致突變性及危害生育力小鼠以口服相當於腸外MRHD(人類最高推薦劑量 劑量之 ketorolac tromethamine 維持 18 個月的研究及大鼠口服腸外 MRHD 2.5 倍劑量為期 24 個研究，皆未顯示引發腫瘤。

Ames 試驗、未經規劃之 DNA 合成與修復及前瞻性突變檢定分析中，ketorolac tromethamine 不會引發突變；於試管試驗小鼠微核檢定分析中不會造成染色體斷裂；於 1590 μg/ml(約為平均人類血漿濃度之 1000 倍)及更高濃度時 ketorolac tromethamine 可能提高中國倉鼠卵巢細胞之染色體畸形分裂之發生率。

雄性或雌性大鼠分別口服 9 mg/kg（53.1mg/m^2）及 16 mg/kg（94.4mg/m^2）劑量，並未危害生育力。

用於孕婦：

對兔使用 3.6 mg/kg（42.35mg/m^2）每日口服劑量及大鼠使用 10 mg/kg（59mg/m^2）於器官發生期間進行生殖研究，研究結果並未造成胎兒畸型，ketorolac tromethamine 口服劑量 1.5 mg/kg（8.8mg/m^2），乃人類口服劑量之半，於大鼠妊娠 17 日後投藥引發難產及幼鼠死亡率增高；並無用於孕婦之充分且經過徹底對照研究，故唯有於潛在效益超過對胚胎之潛在風險時方可用於孕婦。由於已知前列腺素抑制性藥物對胎兒心血管的影響(動脈導管閉合)，因此於懷孕末期禁忌使用本品。

用於哺乳婦：本品投予哺乳婦時應審慎。

用於兒童：用於兒童的安全性及療效仍未確立。

副作用：

對照臨床研究中最常報告的副作用為滴注時的暫時性針刺感與燒灼感，發生率約佔接受治療病人之 40%；所有藥物開發研究中，其它副作用發生率包括，眼部刺激（3%）、過敏反應（3%）、眼部淺層感染（0.5%）及角膜表面發炎（1%）。

用法用量：本藥須由醫師處方使用

本品推薦劑量為每日四次，每次一滴(0.25 mg)用於緩解因季節性過敏性結膜炎引發的眼部搔癢。

用於治療接受白內障摘除術病人之術後發炎或炎性反應，於白內障手術後 24 小時開始，於患部眼睛滴注，每日四次，每次一滴，並持續直至手術後 2 週。

包裝：

愛克樂®眼藥水(ketorolac tromethamine ophthalmic solution)為局部眼部投藥用之0.5%無菌溶液，為白色不透明塑膠瓶，有 3ml, 5ml,10ml 等三種包裝。

避光儲存於 15℃-25℃。置於兒童不能及之處。

製造廠

Allergan Pharmaceuticals Ireland
Castlebar Road, Westport, County Mayo, Ireland

藥商

香港商愛力根有限公司台灣分公司
台北市羅斯福路二段 102 號 9 樓

FRONT

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BACK

ACULAR®

ALLERGAN

ketorolac tromethamine 0.5%
sterile ophthalmic solution

DESCRIPTION

Each mL contains: ketorolac tromethamine 5 mg with: benzalkonium chloride 0.1 mg, edetate disodium 1 mg, octoxynol 40, sodium chloride and purified water.

ANIMAL PHARMACOLOGY

Ketorolac tromethamine prevented the development of increased intraocular pressure induced in rabbits with topically applied arachidonic acid. Ketorolac did not inhibit rabbit lens aldose reductase *in vitro*.
Ketorolac tromethamine ophthalmic solution did not enhance the spread of ocular infections induced in rabbits with *Candida albicans, Herpes simplex* virus type one or *Pseudomonas aeruginosa*.

CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory and anti-pyretic activity. The mechanism of its action is thought to be due, in part, to its ability to inhibit prostaglandin biosynthesis. Ocular administration of ketorolac tromethamine reduces prostaglandin E_2 levels in aqueous humor. The mean concentration of PGE_2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving 0.5% ACULAR® ophthalmic solution.
Ketorolac tromethamine given systemically does not cause pupil constriction.
Results from clinical studies indicate that ACULAR® ophthalmic solution has no significant effect upon intraocular pressure.
Two controlled clinical studies showed that ACULAR® ophthalmic solution was significantly more effective than its vehicle in relieving ocular itching caused by seasonal allergic conjunctivitis.
Two controlled clinical studies showed that patients treated for two weeks with ACULAR® ophthalmic solution were less likely to have measurable signs of inflammation (cell and flare) than patients treated with its vehicle.
Two drops (0.1 mL) of 0.5% ACULAR® ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL).
One drop (0.05 mL) of 0.5% ACULAR® ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye tid in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at Day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.
ACULAR® ophthalmic solution has been safely administered in conjunction with other ophthalmic medications, such as antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics.

INDICATIONS AND USAGE

ACULAR® ophthalmic solution is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR® is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

CONTRAINDICATIONS

ACULAR® ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

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

PRECAUTIONS

General: It is recommended that ACULAR® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time. ACULAR® should not be administered to patients wearing contact lenses.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice at oral doses of ketorolac tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorigenicity.
Ketorolac tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 ug/mL (approximately 1000 times the average human plasma levels) and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.
Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (53.1 mg/m²) and 16 mg/kg (94.4 mg/m²) respectively.

Pregnancy: Reproduction studies have been performed in rabbits using daily oral doses at 3.6 mg/kg (42.35 mg/m²) and in rats at 10 mg/kg (59 mg/m²) during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (8.8 mg/m²), which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus) the use of ACULAR® ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when ACULAR® is administered to a nursing woman.

Pediatric Use: Safety and efficacy in children have not been established.

ADVERSE REACTIONS

In patients with allergic conjunctivitis the most frequent adverse events reported with the use of ACULAR® ophthalmic solution have been transient stinging and burning on instillation. These events were reported by approximately 40% of patients treated with ACULAR® ophthalmic solution. In all development studies conducted other adverse events reported during treatment with ACULAR® include ocular irritation (3%), allergic reactions (3%), superficial ocular infections (0.5%) and superficial keratitis (1%).

DOSAGE AND ADMINISTRATION

The recommended dose of ACULAR® ophthalmic solution is one drop (0.25 mg) four times a day for relief of ocular itching due to seasonal allergic conjunctivitis. For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of ACULAR® ophthalmic solution should be applied to the affected eye(s) four times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

HOW SUPPLIED

ACULAR® (ketorolac tromethamine) ophthalmic solution is available for topical ophthalmic administration as a 0.5% sterile solution and is supplied in white opaque plastic bottles in the following sizes: 3 mL, 5 mL, 10 mL.
Note: Store between 15° - 25°C; protect from light. On prescription only. Keep out of the reach of children.

ALLERGAN

Manufactured by: Allergan Pharmaceuticals Ireland, Westport, Ireland.
ACULAR® is a registered trademark of Syntex Pharma Ag.

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