Nursing Mothers: A study in lactating rats revealed excretion of epinine in the breast milk. 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 RELESTAT™ ophthalmic solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported ocular adverse events occurring in approximately 1 - 10% of patients were burning sensation in the eye, folliculosis, hyperemia, and pruritus. The most frequently reported non-ocular adverse events were infection (cold symptoms and upper respiratory infections) seen in approximately 10% of patients, and headache, rhinitis, sinusitis, increased cough, and pharyngitis seen in approximately 1 - 3% of patients.

Some of these events were similar to the underlying disease being studied.

DOSEAGE AND ADMINISTRATION
The recommended dosage is one drop in each eye twice a day.

Treatment should be continued throughout the period of exposure (i.e., until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED
RELESTAT™ (epinine HCI ophthalmic solution) 0.05% is supplied sterile in opaque white LDPE plastic bottles with dropper tips and white high impact polystyrene (HIPS) caps as follows:
5 mL in 8 mL bottle


Rx Only

Manufactured by
Allergan Pharmaceuticals Ireland
Castletub Road, Wexport
County Mayo
Ireland

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RELESTAT™ (epinine HCI ophthalmic solution) 0.05%

Sterile

DESCRIPTION
RELESTAT™ (epinine HCI ophthalmic solution) 0.05% is a clear, colorless, sterile isotonic solution containing epinine HCI, an antihistamine and an inhibitor of histamine release from the mast cell for topical administration to the eyes.

Epinine HCI is represented by the following structural formula:

![Epinine HCI Structure](image)

C₈H₁₃NO₃ | HCl Mol. Wt. 285.78

Chemical Name: 3-Amino-9, 13b-dihydro-11H-dibenzo[f,j]imidazo[1,5-a] azepine hydrochloride

Each mL contains: Active: Epinine HCI 0.05% (0.5 mg/mL) equivalent to epinine 0.04% (0.44 mg/mL). Preservative: Benzalkonium chloride 0.01%; Inactive: Edetate disodium, purified water; sodium chloride; sodium phosphate, monobasic; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). RELESTAT™ has a pH of approximately 7 and an osmolality range of 250 to 310 mOsm/kg.

CLINICAL PHARMACOLOGY
Epinine is a topical, active, direct H₁-receptor antagonist and an inhibitor of the release of histamine from the mast cell. Epinine is selective for the histamine H₁-receptor and has affinity for the histamine H₂-receptor. Epinine also possesses affinity for the α₁-, α₂-, and 5-HT₂A-receptors. Epinine does not penetrate the blood-brain barrier and, therefore, is not expected to induce side effects of the central nervous system.

Fourteen subjects, with allergic conjunctivitis, received one drop of RELESTAT™ ophthalmic solution in each eye twice daily for seven days. On day seven average maximum epinine plasma concentrations of 0.04 - 0.014 ng/mL were reached after about two hours indicating low systemic exposure. While these concentrations represented an increase over those seen following a single dose, the day 1 and day 7 Area Under the Curve (AUC) values were unchanged indicating that there is no increase in systemic absorption with multiple dosing. Epinine is 64% bound to plasma proteins. The total systemic clearance is approximately 56 L/hr and the terminal plasma elimination half-life is about 12 hours. Epinine is mainly excreted unchanged. About 55% of an intravenous dose is recovered unchanged in the urine with about 30% in feces. Less than 10% is metabolized. The renal elimination is mainly via active tubular secretion.

Clinical studies: Epinine HCI 0.05% has been shown to be a significantly superior vehicle for improving ocular itching in patients with allergic conjunctivitis in clinical studies using two different models: (1) conjunctival antigen challenge (CAC) where patients were dosed and then received antigen instilled into the inferior conjunctival fornix; and (2) environmental field studies where patients were dosed and evaluated during allergy season in their natural habitat. Results demonstrated a rapid onset of action for epinine HCI 0.05% within 3 to 5 minutes after conjunctival antigen challenge. Duration of effect was shown to be 8 hours, making a twice daily regimen suitable. This dosing regimen was shown to be safe and effective for up to 8 weeks, without evidence of tachyphylaxis.

INDICATIONS AND USAGE
RELESTAT™ ophthalmic solution is indicated for prevention of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS
RELESTAT™ ophthalmic solution is contraindicated in those patients who have shown hypersensitivity to epinine or to any of the other ingredients.

WARNINGS
RELESTAT™ is for topical ophthalmic use only and not for injection or oral use.

PRECAUTIONS
Information for Patients: Patients should be advised not to wear a contact lens if their eye is red. RELESTAT™ ophthalmic solution should not be used to treat contact lens related irritation. The preservative in RELESTAT™ benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed prior to instalation of RELESTAT™ ophthalmic solution and may be reinserted after 10 minutes following its administration.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Bottle should be kept tightly closed when not in use.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In 14-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinine was not carcinogenic at doses up to 40 mg/kg (approximately 30,000 times higher than the maximum recommended ocular human dose of 0.0014 mg/kg/day (MOHD) on a mg/kg basis, assuming 100% absorption in humans and animals).

Epinine in newly synthesized batches was negative for mutagenicity in the Ames/Salmonella assay and in vitro chromosome aberration assay using human lymphocytes. Positive results were seen with early batches of epinine in two in vitro chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with H9 cells, respectively. Epinine was negative in the in vitro clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinine was also negative in the cell transformation assay using Syrian hamster embryo cells. V79/HGPRT mammalian cell point mutation assay, and in vivo in vitro unscheduled DNA synthesis assay using rat primary hepatocytes.

Epinine had no effect on fertility of male rats. Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MOHD.

Pregnancy: Teratogenic Effects: Pregnancy Category C
In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was approximately 150,000 times the MROD. Total resorptions and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was approximately 55,000 times the MROD. In both studies, no drug-induced teratogenic effects were noted.

Epinine reduced pup body weight gain following an oral dose to pregnant rats that was approximately 90,000 times the MROD.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, RELESTAT™ ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.