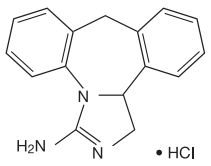
2998

銳視代®眼用液劑
RELESTAT® Ophthalmic Solution 0.05%
(epinastine HCl)
衛署藥輸字第024332號

FRONT

性狀
RELESTAT®（epinastine HCl眼用液劑）0.05%是含有epinastine HCl的透明無色無菌等張溶液，可供局部眼部投藥，epinastine HCl屬於抗組織胺，且係抑制組織胺由肥大細胞釋放的抑制劑。

Epinastine HCl可以如下結構式表示：



$C_{16}H_{15}N_3 \bullet HCl$ Mol. Wt. 285.78

化學名：3-Amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride

每毫升含： 活性成分 ：Epinastine HCl 0.05%(0.5 mg/mL)
相當於epinastine 0.044%(0.44 mg/mL)；
保存劑 ：Benzalkonium chloride 0.01%；
無活性成分 ：EDTA二鈉、純水、氯化鈉、一鹼基磷酸鈉、及氫氧化鈉及/或鹽酸（用來調整pH值）。

RELESTAT® pH值約等於7，以及滲透壓介於250至310 mOsm/kg之範圍。

臨床藥理
Epinastine是一種可作用於局部部位的直接組織胺H1-受體拮抗劑，且是抑制組織胺由肥大細胞釋放組織胺的抑制劑；epinastine對組織胺H1-受體具有選擇性，對組織胺H2-受體具有親和力，也對α1受體、α2受體，以及5-HT2-受體具有親和力；epinastine不會通過血腦障壁，因此預期不會誘發中樞神經系統副作用。

14位患有過敏性結膜炎病人每日兩次，每次兩眼各滴一滴RELESTAT®眼用液劑，連續7日；於第7日，約2小時後，達到平均最高epinastine血漿濃度0.04±0.014奈克/毫升，表示全身性暴露量低；雖然此種濃度比單次劑量後的血漿濃度高，但第1日與第7日的曲線下方面積（AUC）值不變，表示使用多次給藥，不會造成全身性吸收的增加。epinastine與血漿蛋白的結合率是64%，總系統廓清率約為每小時56升，終端血漿清除半衰期約12小時；epinastine主要係以未經改變的形式排泄，靜脈注射劑量約有55%在尿液中以未改變形式回收，糞便的回收比率約30%，代謝比率低於10%，腎臟清除作用主要係透過主動腎小管分泌作用清除。

臨床研究：使用兩種不同研究模型，epinastine HCl 0.05%用於患有過敏性結膜炎病人的臨床研究，顯示改善眼睛搔癢的效果顯著優於媒劑，亦即下述兩種研究模型：（1）結膜抗原暴露研究模型（Conjunctival Antigen Challenge, CAC），此種研究模型中，對病人投藥，然後病人接受抗原滴注於內結膜穹窿（inferior conjunctival fornix）；以及（2）環境自然研究模型（environmental field studies），本研究中對病人給藥，於過敏季節於病人的自然居住地做評比。臨床研究結果證實epinastine HCl 0.05%的作用起始迅速，於結膜抗原暴露（CAC）後的3分鐘至5分鐘內開始產生作用，功效持續時間8小時，因此適合採用每日投藥兩次；根據臨床試驗結果，用藥長達8週安全有效，並無藥物耐受性的狀況出現。

適應症
減緩過敏性結膜炎所引起的眼睛搔癢。

禁忌
RELESTAT® 眼用液劑禁忌用於對epinastine或製劑中的任何其它成分過敏病人。

警語
RELESTAT® 限供局部眼用，不可供注射用或口服使用。

注意事項
病人資訊：須告知病人，於眼睛泛紅時，勿佩戴隱形眼鏡，RELESTAT®眼用液劑禁忌用來治療隱形眼鏡所引起的刺激；RELESTAT®所含保存劑，亦即benzalkonium chloride可能被軟式隱形眼鏡吸收，因此滴注RELESTAT®眼用液劑之前，應取下隱形眼鏡，而在滴注眼藥水後10分鐘後，才可重新戴上隱形眼鏡。

應指導病人，避免眼藥水瓶的滴注器梢端接觸眼球、眼球周圍結構、手指、或任何其它表面，以避免眼藥水受到已知會引起眼部感染的常見細菌污染；使用受污染的溶液可能導致眼睛嚴重損傷，因而導致失明。

不用時，眼藥水瓶須緊密封閉。

致癌作用、致突變發生、生育力受損：
分別對小鼠或大鼠進行為期18個月或為期兩年的膳食致癌作用研究，epinastine於高達40毫克/每公斤體重劑量[該劑量比人類最高推薦眼用劑量

0.0014毫克/每公斤體重/日（MROHD）高約30,000倍（以毫克/每公斤體重為基準），假設epinastine於人體及動物體百分之百吸收]時，不具有致癌作用。

新近合成批次的epinastine用於Ames/Salmonella（沙門氏桿菌）檢定分析以及使用人類淋巴細胞進行體外染色體異常檢定分析，epinastine的致突變性呈陰性反應；1980年代，分別使用人類周邊淋巴細胞、以及使用V79細胞進行體外染色體異常研究，早期批次的epinastine呈現陽性反應；在體內致染色體斷裂發生研究中，包括小鼠微核檢定分析、以及中國倉鼠的染色體異常檢定分析，epinastine皆呈陰性反應；在使用敘利亞倉鼠胚細胞的細胞轉形檢定分析、V79/HGPRT哺乳動物細胞點突變檢定分析、和使用大鼠肝細胞進行體內/體外非排定DNA合成檢定分析，epinastine也呈現陰性反應。

Epinastine對雄大鼠的繁殖力不會造成影響；雌大鼠於口服劑量高達約90,000倍MROHD時，觀察到生育力下降。

懷孕致畸胎性：懷孕分級C
在懷孕大鼠的胚胎發育研究中，於約150,000倍MROHD口服劑量，觀察到母體毒性，但未見胚胎影響。孕兔以約55,000倍MROHD的口服劑量進行胚胎發育研究觀察到胚胎完全再吸收且流產的現象；兩項研究中皆未見藥物相關之致畸胎性。

懷孕大鼠給予高達約90,000倍MROHD口服劑量後，epinastine會減少幼鼠體重的增加。

目前對於孕婦並無合適並含適當對照組的研究，且由於動物生殖研究並非經常能預測人類反應，因此RELESTAT®眼用液劑唯有於判定可能的效益超越對胎兒可能造成的風險時才可用於孕婦。

用於哺乳的母親：使用泌乳的大鼠進行研究，顯示epinastine分泌於乳汁中，未知epinastine是否分泌於人類乳汁；由於多種藥物皆可能分泌於人類乳汁，因此對哺乳婦女投予RELESTAT®眼用溶液劑時須審慎。

用於小兒：本品用於3歲以下小兒病人的安全性及有效性尚未確立。

用於老人：年長病人與年輕病人間並未觀察得安全性及有效性有任何總體上差異。

不良反應
最常報告的眼部不良反應，發生率約1%-10%，如後：眼睛燒灼感、濾泡過度增殖、充血、及搔癢。

最常報告的非眼部不良反應是感染（感冒症狀、上呼吸道感染），發生率約10%；而頭痛、鼻炎、鼻竇炎、咳嗽、和咽喉炎的發生率約1-3%。

若干不良反應與已進行之臨床研究所得知的可能病例相似。

用法用量：本藥須由醫師處方使用
建議用法用量為每日兩次，每次兩眼各滴1滴。

治療期間即使症狀已消失，不宜貿然停藥，請依醫師指示決定用藥期限。

包裝
RELESTAT®（epinastine HCl眼用液劑）0.05%乃不透明白色LDPE塑膠瓶無菌包裝，塑膠瓶附有滴注器梢端、和白色高度耐衝擊性聚苯乙烯（HIPS）瓶蓋：5ml瓶裝。

儲存：儲存於 25℃ 以下，瓶蓋維持緊閉且置於兒童不能接觸到之處。

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

- Part number 72052UT12B
- Drawing number 0284201
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- Page 1 of 2

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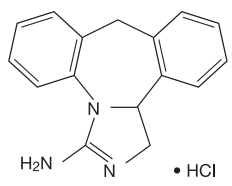
RELESTAT®

(epinastine HCl ophthalmic solution) 0.05%
Sterile

BACK

DESCRIPTION

RELESTAT® (epinastine HCl ophthalmic solution) 0.05% is a clear, colorless, sterile isotonic solution containing epinastine HCl, an antihistamine and an inhibitor of histamine release from the mast cell for topical administration to the eyes.
Epinastine HCl is represented by the following structural formula:



$C_{16}H_{15}N_3$ HCl Mol. Wt. 285.78
Chemical Name: 3-Amino-9, 13b-dihydro-1H-dibenz[c,f] imidazo[1,5-a] azepine hydrochloride
Each mL contains: Active: Epinastine HCl 0.05% (0.5 mg/mL) equivalent to epinastine 0.044% (0.44 mg/mL); **Preservative:** Benzalkonium chloride 0.01%; **Inactives:** 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

Epinastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from the mast cell. Epinastine is selective for the histamine H_1-receptor and has affinity for the histamine H_2-receptor. Epinastine also possesses affinity for the α1-, α2-, and 5-HT_2-receptors. Epinastine 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 epinastine 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. Epinastine 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. Epinastine 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: Epinastine HCl 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 epinastine HCl 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 epinastine 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 instillation 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 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine 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 (MROHD) on a mg/kg basis, assuming 100% absorption in humans and animals].

Epinastine 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 epinastine in two *in vitro* chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively. Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine 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.

Epinastine 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 MROHD.

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 MROHD. Total resorptions and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was approximately 55,000 times the MROHD. In both studies, no drug-induced teratogenic effects were noted. Epinastine reduced pup body weight gain following an oral dose to pregnant rats that was approximately 90,000 times the MROHD.

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.

Nursing Mothers: A study in lactating rats revealed excretion of epinastine 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.

DOSAGE 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® (epinastine HCl 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 10 mL bottle

Storage: Store below 25°C. Keep bottle tightly closed and out of the reach of children.

Rx Only

Manufactured by
Allergan Pharmaceuticals Ireland
Castlebar Road, Westport
County Mayo
Ireland
 9343X

Licensed from Boehringer Ingelheim Int. GmbH

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