SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Opatanol. For information on changes after approval please refer to module 8.

1. Introduction

Allergic conjunctivitis is an allergen induced inflammatory response, which usually affects adults between 20 and 40 years of age. Patients may be allergic to substances such as airborne allergens, drugs, cosmetics or contact lens products although the specific cause may not always be found. Upon exposure to a specific allergen, allergic patients elicit a hypersensitivity response, which may take minutes or even days to manifest. Symptoms and signs of allergic conjunctivitis include itching (either intermittent or constant) located under the superior eyelid or inner canthus, injection (redness, hyperaemia) of conjunctiva, chemosis, discharge and tearing. Intermittent episodes may evolve into constant symptoms and an associated rhinitis may occur.

Seasonal allergic conjunctivitis (SAC) and Perennial Allergic Conjunctivitis (PAC) are the most prevalent forms of " allergic conjunctivitis". Allergic rhino conjunctivitis accounts for more than half the cases of ocular allergy although many patients only present with the ocular symptoms.

SAC and PAC have been classified as type 1 mast cell dependent IgE mediated immune hypersensitivity reactions and exposure to environmental antigens stimulates the immune system to produce specific IgE antibodies which bind to the surface of mast cells and sensitise them. With subsequent exposure, allergens traverse the tear film and come in contact with the sensitised mast cells initiating degranulation of these cells, and so release of the chemical mediators responsible for the inflammatory response. Histamine is the cardinal mediator responsible for the signs and symptoms of SAC.

Olopatadine is a new dibenzoxipine derivative developed initially for systemic treatment of allergic rhinitis, urticaria, and bronchial asthma and developed by this applicant as a topical anti-allergic agent (OPATANOL 1 mg/ml eye drops, solution; hereafter referred to as OPATANOL), which is a selective antihistamine (at the end organ) and also thought to be an inhibitor of the release of histamine and other pro-inflammatory mediators from the mast cell. It is considered to have high affinity for the histamine H_1 receptor and no effect on alpha-adrenergic and serotonin receptors.

OPATANOL is indicated in the treatment of ocular signs and symptoms of seasonal allergic conjunctivitis.

The recommended posology is one drop of OPATANOL in the conjunctival sac of the affected eye(s) twice daily (8 hourly). Treatment may be maintained for up to four months, if considered necessary.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

OPATANOL eye drops is a 1mg/ml (0.1%w/v) solution of olopatadine as the hydrochloride salt. The composition is adequately described and consists of known pharmaceutical excipients routinely used in eye drop formulations: i.e. sodium chloride (tonicity), benzalkonium chloride (preservative, equivalent to 0.01%w/v), disodium phosphate dodecahydrate (buffering agent), hydrochloric acid and/or sodium hydroxide to adjust the pH and purified water as the solvent. Up to 3 % overage of benzalkonium chloride is used to compensate for loss during manufacture.

The sterile solution is packaged in a 5 ml opaque LDPE bottle with a clear LDPE dispensing plug and white polypropylene closure. The bottle is tamper-evident.

Active substance

Olopatadine (INN) is present as the hydrochloride salt.

Information on this active substance has been provided in the form of an EDMF, with letter of access. The synthesis of olopatadine is well established as this product had been marketed in the U.S. for 4 years at the time of submission of the EU dossier. The synthetic route is a 5 step process followed by a 3 step purification sequence ending in crystallisation from acetone. Proof of structure has been established by means of the usual spectroscopic techniques - UV, IR, ^{1}H and ^{13}C- NMR and mass

spectra. The configuration about the $C_{11} – C_1$ double bond which determines geometrical isomerism was determined by the Nuclear Overhauser Effect (NOE) in the ^{1}H-NMR ^{13}C-NMR spectrum and confirmed by X-ray diffraction analysis.

DSC and Powder X-ray analysis on product recrystallised from a range of solvents indicate that there are no polymorphs. However, polymorphism is not important in this case as olopatadine is in solution in the finished product.

Olopatadine has no chiral centres but can exist as two geometric isomers. The preferred configuration for optimal pharmacological activity is the *Z*- isomer (CIP convention). The *E*- configuration is a contaminant and degradant, and is controlled in the active substance at less than 0.1%.

Active substance specification

The active substance specification includes tests for identity, assay (HPLC (99-101%)) and a number of purity tests for related substances (max. 0.25%), residual acetone (GC, 1000ppm) etc. Considering the use of olopatadine in an ophthalmic product, the specification reasonably also includes a test for microbial bioburden (PhEur).

Batch analytical data are presented on 10 production scale batches and 3 development batches, all indicating compliance with the specification and good uniformity and control of the synthetic process.

Stability

The stability of the active substance has been investigated under stressed conditions which indicate that it is resistant except under high stress. Potential degradants are the *E*- isomer , another degradant which is only formed under highly stressed conditions (in solution at pH 10, 40°C). The structure has been elucidated and is provided. In addition 'SOX' (an intermediate in the synthesis of olopatadine) and the N-oxide (a metabolite) are also named as potential degradants in solution.

Long term ICH stability studies were conducted by the active ingredient manufacturer on 6 production scale batches at 25°C/60% RH for up to 42 months and 40°C/75% RH for up to 6 months. The study included 2 container types: a double polyethylene bag in a paper bag and a double polyethylene bag in a metal can (3 recent batches). Methods are validated and stability indicating. They include assay, related substances (TLC and HPLC), pH, appearance of solution and loss on drying. The active ingredient indicates no trend for instability, and all test results after 39 months at 25°C comply with the specification. Similarly all results comply with the specification after 6 months at 40°C. Total related substances are below 0.1%. Therefore, on this basis the proposed re-test period of 36 months is acceptable.

Other ingredients

All excipients are tested to and meet current PhEur. requirements. In addition all excipients (except Sodium Hydroxide and Hydrochloric acid) are tested for bioburden with a limit of NMT 100 CFU/g. The bioburden limit for purified water is NMT 1CFU/100ml.

Certificates of analyses are provided for each excipient, and documentation is provided from the suppliers declaring that each excipient (1) does not contain any materials of animal origin and (2) did not come in contact with material of animal or human origin during their manufacture. Therefore the excipients are in compliance with Directive 1999/82/EEC on minimising the risk of transmission of TSE.

Specifications (chemical and physical) are also provided for the opaque LDPE bottle, clear LDPE dispensing plug and the white polypropylene cap. All meet the requirements of the PhEur for containers for ophthalmic use and the PhEur monograph for polyolefins. The cap meets the requirements for containers for parenteral use.

Product development and finished product

Development pharmaceutics addresses optimisation of pH, preservative efficacy, choice of excipients and container and method of sterilisation of the eye drops and container. Compatibility of the active ingredient was demonstrated with all excipients used in the formulation. This was done by HPLC analyses of prototype formulations of active and excipients.

The choice of benzalkonium chloride 0.01% as preservative is justified on the basis that it is a broad spectrum antimicrobial agent and has been shown to be safe in ocular tissues. It is widely used in topical ophthalmic products.

The applicant justifies the choice of container on the basis that LDPE bottles are widely used for eye drops. The LDPE bottle offers advantages in terms of patient convenience and compliance but the applicant claims is not suitable for terminal sterilisation. Satisfactory **c**ompatibility studies with the proposed formulation and leaching studies are presented in part IIC of the dossier. No leaching was detected from the proposed pack after 24 hours at 70°C (limit of detection of 1ppm).

Photostability investigations support the choice of an opaque bottle, as the product is light sensitive. Olopatadine solution 0.1% stored in clear ampoules exposed to 1,000 foot-candles at 26 ± 1°C for 7 days (equivalent to 1.25 years of home lighting) exhibited substantial degradation compared to control samples in amber ampoules.

The method of sterilisation proposed for the LDPE container utilises ethylene oxide. Investigations were carried out using OPATANOL Eye Drops Solution packaged in both ethylene oxide and gamma sterilised (5.0 Mrad/50 kGy) containers. Stability results for 52 weeks at 25°C/40% RH and accelerated conditions show significantly greater amounts of degradation products (up to 0.4%) and greater loss in potency in gamma sterilised packaging compared to ethylene oxide sterilised packaging. Negligible levels of degradation products were found in the ethylene oxide sterilised packaging. (Ethylene oxide and related residues comply with current EU guidance).

The bulk eye drop solution is mixed and then sterilised by filtration through two 0.22 μm filters in series, and filled into sterilised containers. The manufacturing process has been validated by a number of studies including media fill runs, and overall the development pharmaceutics is adequately documented and is acceptable for a product of this type.

Product Specification

The specification includes tests by validated methods for identification (TLC and HPLC), assay (standard release limits, i.e. 95-105% by HPLC), degradation products of olopatadine detected in the finished product are N-oxide and SOX. Individual and total impurity limits in the finished product are justified with reference to batch analytical data and toxicology studies, bearing in mind the ophthalmic use of the product. Based on the maximum dose of 0.24 mg/day, the proposed limits are also in compliance with the ICH guideline on impurities in drug products. The release specification for benzalkonium chloride is 90-110%. Sterility, pH, osmolality, and clarity are also tested.

Batch data are provided for 4 production scale batches and indicate satisfactory uniformity.

Stability of the Product

Four batches (2x production scale, 2x smaller) in the market pack manufactured at the proposed manufacturing site were studied, and storage conditions used were based on scientific advice given to the company by the CPMP in 1996. Stability data are presented at 25°C ± 2°C/35-40% RH, 40°C ± 2°C/10-20% RH, 4°C (refrigerated), freeze thaw cycle, temperature cycle (4 to 30°C) and light cabinet (1000 foot candles). Data are available for up to 156 weeks at appropriate test intervals.

Real time and accelerated conditions are more stressful than ICH conditions for semi-permeable containers with respect to relative humidity (25°C ± 2°C/40%±5% RH and 40°C ± 2°C/10-20% RH). The guideline (CPMP/ICH/2736/99, effective June 2001) states that 'ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments', and it was concluded that the storage conditions used meet this requirement.

All batches tested complied with the shelf-life specification. There is an increase in active ingredient content and preservative content over shelf-life most likely due to moisture loss, therefore particular attention has been paid to levels of degradation products.

Degradation product levels are within specification up to 156 weeks at 25°C and for 26 weeks at 40°C. Individual identified degradants N-oxide and SOX are present at justified levels under both conditions. Osmolality, pH, clarity, colour and visual particulates are within specification with very little change.

The product passes the PhEur sterility test at 52, 104 and 156 weeks 'real-time'.

Batches tested under other conditions, (temperature cycling, refrigerated freeze thaw cycle for 6 weeks), showed no significant change with all results were within specification.

Based on these results, the shelf-life and storage conditions as defined in the SPC are justified.

Discussion on chemical, pharmaceutical and biological aspects

The manufacture and control of the active substance and finished product have been investigated and are controlled in a validated way. The pharmaceutical aspects of this product have been well documented and indicate a uniform product with reliably consistent performance in the clinic. The stability of products in semi-permeable containers has a history of being problematical with regard to the relevance of certain low-humidity studies required by the old CPMP/ICH guidelines. However, since the publication of a revised ICH guideline this has been rationalised to some extent, and the company has carried out relevant stability studies in this regard, with satisfactory results.

At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile, e.g. process validation studies were needed to confirm the soundness of the manufacturing process for large-scale batches of product. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

3. Part III: Toxico-pharmacological aspects

Good Laboratory Practices

Most of the studies were conducted under GLP in Japan according to MHW guidelines prior to the implementation of ICH. Although the studies are of an older style they are sufficient in quality, number and type, to assess the pharmaco/toxicologic profile of olopatadine in laboratory animals.

Pharmacodynamics

- *In vitro* studies

In vitro receptor binding studies and functional potency studies in whole (intact) cells have demonstrated the affinity and selectivity of olopatadine for the histamine H_1 receptor. Olopatadine has a higher selectivity for the histamine H_1 receptor over H_2 and H_3 receptors than reference anti-histamines (ketotifen, levocabastine, antazoline, pheniramine). In human ocular cells possessing histamine H_1 receptors, olopatadine inhibits histamine-induced phosphoinositide-turnover (IC_{50} = 9-39 nM). In human conjunctival epithelial cells, olopatadine prevented the secretion of the pro-inflammatory cytokines IL-6 and IL-8 following histamine stimulation (IC_{50} = 5.5 nM & 1.7 nM, respectively).

In separate studies, the affinity of two metabolites (the N-desmethyl and N-didesmethyl forms) for the histamine-H_1 receptor was 1.5-2.0 fold lower than that of the parent compound.

Olopatadine inhibits the release of histamine from human conjunctival mast cells *in vitro* (IC_{50} = 559 μM). This compares favourably with other marketed agents in the same model; cromolyn sodium, nedocromil, N-acetylaspartyl glutamic acid and ketotifen. In a separate study, olopatadine-N-oxide, the main metabolite in man, also inhibited histamine release, though less potently, with an IC_{50} of 3.07 mM. Olopatadine also inhibits the release of the pro-inflammatory cytokine TNFα from human conjunctival mast cells (IC_{50} = 13.1 μM), suggesting that the compound may limit the sustained inflammatory cell infiltration observed in chronic allergic eye disease.

- *In vivo* studies

The guinea pig model of passive conjunctival anaphylaxis (PCA) was used to demonstrate the topical ocular efficacy of olopatadine. Administered prior to topical ocular antigen challenge, olopatadine reduced the severity of the immediate hypersensitivity response. Similarly, histamine-induced increases in vascular permeability were inhibited. Onset of action is somewhat slower than

emedastine. Duration of action data suggests that the effectiveness of olopatadine 0.1% did not diminish significantly through 24 hours.

The anti-allergic activity of oral olopatadine was studied in models of PCA in rats. The response to topically applied antigen was significantly and dose-dependently inhibited by olopatadine. The inhibitory activity was higher for olopatadine than for other anti-allergic agents in the same model. Olopatadine also showed stronger activity than other anti-allergics in models of antigen-induced bronchoconstriction, in inhibition of lethal anaphylactic shock, in inhibition of allergic pleurisy, and in inhibiting allergic late phase reaction.

- Pharmacodynamic drug interactions

In studies of drug interaction, the inhibitory activity of olopatadine on the metabolism of six cytochrome P-450 (CYP) isozyme specific substrates was determined in human liver microsomes. Olopatadine did not inhibit the metabolism of any isozyme specific substrate tested at concentrations that were 4 orders of magnitude higher than in humans after ocular administration of 0.15% olopatadine ophthalmic solution.

- General and safety pharmacology programme

The general pharmacology included studies on *in vitro* selectivity, on nervous system, on cardiovascular and respiratory effects, and on QT-prolonging effects.

The CNS studies indicated that the potential for CNS effects after olopatadine treatment will be minimal.

The cardiovascular studies showed that olopatadine did not produce any notable change in respiratory rate, heart rate and ECG in dogs at IV doses of 0.1 and 0.3 mg/kg. At 5 mg/kg, there were temporary increases in respiratory rate and heart rate. At high doses, a decrease in blood pressure and increase in heart rate were noted. Blood flow of the femoral artery and peripheral blood vascular resistance also decreased. To evaluate the prolonged effects of olopatadine on the cardiovascular system as assessed by ECG, heart rate and blood pressure, doses from 3 to 100 mg/kg were given orally to conscious dogs. A significant QTc prolongation caused by 100 mg/kg olopatadine was considered to be an apparent effect caused by increase of heart rate. The potential risk of torsade de pointes caused by olopatadine would only be at dosages largely exceeding what will be used clinically. The potential for altered hepatic metabolism and resulting cardiotoxic effects after co-administration of olopatadine with the CYP3A4 inhibiting drug itraconazole was studied in dogs. No difference in heart rate, blood pressure or QT interval were observed between the group receiving olopatadine alone and the group receiving both olopatadine and itraconazole.

- Summary of salient findings

The potential for efficacy of olopatadine in the treatment of allergic conjunctivitis has been demonstrated in a series of *in vitro* and *in vivo* studies. *In vitro* olopatadine HCl has high affinity for the histamine H_1 receptor and may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. *In vivo* olopatadine HCl significantly reduced the allergic response in conjunctival and classical systemic models.

Secondary pharmacodynamic effects, including those on the cardiovascular system, were seen only at doses and exposures well in excess of those anticipated following topical ocular administration in man.

Studies on various metabolising enzymes suggest that drug interactions are unlikely in the cytochrome P450 system.

Pharmacokinetics

A single ocular pharmacokinetic study was performed in rabbits with a 0.15% ophthalmic solution. Systemic exposure was demonstrated, absorption was rapid and plasma concentrations reached maximal levels of 10 ng/ml in 30 minutes. The bioavailability was high (83%). Elimination was biphasic with a half-life of 0.8 hour.

Ocular tissue distribution was studied by dosing of 0.15% ^{14}C-olopatadine ophthalmic solution to rabbits. Radioactivity was rapidly absorbed into the anterior ocular tissues, and maximal tissue levels

were reached within 30-60 minutes. The radioactivity concentrations in ocular tissues decreased rapidly with elimination half-lives of 1-2 hours.

Pharmacokinetics after oral and IV-doses of olopatadine was studied in rats, rabbits, dogs and monkeys. Elimination half-life from plasma was rapid in all animals after IV administration (0.7 hours in rabbits, 5 hours in rats, 7 hours in dogs and 10 hours in monkeys). Oral bioavailability was high in all animals ranging from 70% in the rat to 100% in the monkeys.

Rats were given single 1 mg/kg oral or IV doses of ^{14}C-olopatadine. At 168 hours post dose radioactivity was completely eliminated from most tissues. There was a high level of biliary excretion (45% of dose) and enterohepatic recirculation.

The percentage of olopatadine excreted unchanged in urine after an oral dose of 1 mg/kg was 32%, 58% and 40% in rats, dogs and monkeys, respectively, and in humans given oral doses of 5-80 mg, the percentage was 58.7-73.4%. The urinary elimination as studied in rats and monkeys occurred by both glomerular filtration (20%) and tubular secretion (80%).

In rats given an oral dose of 1 mg/kg ^{14}C-olopatadine, the highest tissue concentration was in the small intestines at 0.5 hours, 22 times the concentration in plasma. Organs involved in metabolism and excretion, and secretory organs showed the highest distribution. Radioactivity in the brain was extremely low.

In a 21-day study in rats, an increase in radioactivity concentration was seen due to repeated administration, with a steady state being reached between the 7th and 14th dose. Whereas the t½ of plasma radioactivity after the single dose administration was about 16 hours, the t½ in the repeated dose 21-day study was 41 hours.

The metabolism of ^{14}C-olopatadine was similar in rats and dogs. Metabolism in rats and dogs consisted of oxidative N-demethylation of the side chain and hydroxylation of the dibenzoxipine ring, its sulfation and further oxidation of the N-atom in the side chain. Similar metabolites were demonstrated in man. The major metabolites in rats and dogs were N-desmethyl-olopatadine and olopatadine N-oxide, respectively. Specific cytochrome P-450 enzymes responsible for olopatadine metabolism have not been determined but this omission is acceptable because of the very low plasma exposure, the very predominant elimination through renal excretion and a large margin of safety.

Distribution in the eye following ocular administration is primarily to the cornea, but levels were detected in all structures tested. In the rabbit, increased exposure of pigmented tissue (iris/ciliary body) was noted in terms of higher Cmax (2-fold) and T½ (10-fold).

Exposure was demonstrated in the foetus and milk of lactating rats. Kinetic parameters appear to run parallel in both dam and foetus.

In summary, oral and topical pharmacokinetics were similar in all relevant species. Absorption, distribution and elimination are rapid and biphasic. Exposure appears to be dose proportional to a threshold level that exceeds likely clinically relevant levels in all species. The role of cytochrome P450 enzymes in olopatadine HCl metabolism has not been elucidated fully. Elimination is mainly in the urine and bile.

Toxicology

Acute dose toxicology studies were old and of poor quality, and did not contribute useful information to the assessment process. Adverse clinical signs in repeated dose toxicology studies included; reduced body weight gain, mydriasis, blepharoptosis, relaxed scrotum, conjunctival hyperaemia and oral mucosal dryness. Post-mortem findings included; reduced relative weight of the heart and prostate, also interstitial nephritis, fatty vacuolar degeneration of the liver, the renal tubular epithelium and the pancreatic ductular epithelium and hypocellular bone marrow. Severity of findings correlated with both dose and duration of treatment. In all cases effects were seen only at high oral doses, with exposures well in excess of anticipated clinical levels.

Topical ocular studies in rabbits (1 and 6 month studies) and monkeys (6 month study) showed no long term adverse effects. Based on available pre-clinical data, together with clinical experience, adverse effects related to prolonged anti-cholinergic effect and potentials for cataractogenesis or for optic nerve damage are not expected.

Additional local tolerance studies suggest that olopatadine is non-sensitising and non-antigenic. The dermal sensitisation potential of olopatadine was evaluated in guinea pigs. In this study, 75% olopatadine HCl in propylene glycol did not act as a contact sensitiser in the guinea pigs. A study was conducted to investigate if olopatadine might be antigenic by binding to high molecular proteins and thus acting as a haptene. It was concluded that olopatadine showed no antigenicity either alone or in combination with protein in the passive anaphylaxis test, in the *in vitro* passive hemagglutination test and in the systemic anaphylaxis test.

Studies were conducted to investigate the effects of olopatadine on fertility, general reproductive capacity, foetal development and early postnatal growth and development. In the fertility study, oral doses of up to 400 mg/kg/day were given to rats. The peri- and postnatal toxicity studies were done in rats at oral doses up to 600 mg/kg. Reproductive toxicity studies showed adverse effects on the pups (e.g. low birth weight) at high oral doses, associated with maternal toxicity. No teratogenic potential was shown in rats at 600 mg/kg and in rabbits at 400 mg/kg. Adverse effects were seen at non-materna-toxic doses in lactation studies (e.g. poor weight gain and survival, delayed development). It was demonstrated that this was due to secretion of the drug in the milk and subsequent dosing of the pups. Caution should be exercised when prescribing OPATANOL to pregnant women. OPATANOL is not recommended for breast-feeding mothers.

A battery of mutagenicity studies (bacterial reverse mutation assay, the chromosomal aberration test, and the micronucleus test) was conducted and all were negative when testing mutagenicity of olopatadine.

Rat (104 weeks) and mouse (78 weeks) oncogenicity studies were performed. It was concluded that olopatadine showed no carcinogenic potential in mice at doses up to 500 mg/kg/day and in rats at doses up to 200 mg/kg/day. Thickened stomach walls were observed in male mice at 500 mg/kg/day, which appeared to be associated with high, continuous, oral dosing and not associated with an oncogenic response. The finding bears no relevance for carcinogenic risk to man in the current indication.

Discussion on toxico-pharmacological aspects

In toxicology studies, effects were seen only at high oral doses, with exposures well in excess of anticipated clinical levels. Topical ocular studies in rabbits and monkeys showed no long-term adverse effects. Based on available pre-clinical data, together with clinical experience, adverse effects related to prolonged anti-cholinergic effect and potentials for cataractogenesis or for optic nerve damage are not expected. Adverse effects were seen at non-materna-toxic doses in lactation studies, therefore OPATANOL should not be recommended for breast-feeding mothers. In an old, but adequate, series of studies, olopatadine was shown to be non-genotoxic and non-carcinogenic.

4. Part IV: Clinical aspects

The clinical trials in this submission were performed according to GCP standards and agreed international ethical principles.

The clinical development program consists of 28 studies that involved 2587 subjects. The studies were conducted in the period 1993-2000. Apart from one cardiovascular safety study, which was conducted with an oral formulation of olopatadine, all studies were conducted with an ophthalmic formulation. There were 15 studies assessing pharmacodynamic and pharmacokinetic aspects of olopatadine, including 7 conjunctival allergen challenge (CAC) studies and a dose-response study. Five studies assessed efficacy, 4 of these being pivotal studies. Three safety studies were conducted, two of these using a higher daily dose than the one recommended in the SPC, the third one being the above mentioned cardiovascular safety study. Moreover, 5 studies were carried out in other indications than SAC (vernal conjunctivitis); these studies are included in the safety evaluation.

Clinical pharmacology

Pharmacodynamics

- ***Dynamic studies***

The principle in the CAC test is as follows: Patients with an established history of SAC and with a positive skin test/RAST are given a predetermined topical ocular dose of the allergen to induce a reaction. This allergic clinical reaction is consistent with the "naturally" occurring allergic reaction with mast cell degranulation, release of mediators and clinical signs (e.g. redness) and symptoms (e.g. itching) which can be quantified and which are reproducible. The provoked reaction can be used to evaluate any allergic topical ocular products, with the patient acting as his/her own control. The clinical signs and symptoms are evaluated at predetermined times after the challenge. The test medication can be compared to placebo, or an active comparator as medication can be applied bilaterally.

The conjunctival allergen challenge (CAC) test is a validated model for studying allergic conjunctivitis. It provides standardised reproducible results, thereby avoiding the variability in symptoms and signs inherent in the naturally occurring condition. Seven CAC studies were presented in the clinical programme. The following figure gives an outline of the CAC studies. Efficacy parameters were: Ocular redness (0-12 scale) assessed, and ocular itching (0-4 scale, none-extremely severe) recorded prior to and 3, 10 and 20 minutes after each CAC.

Study	Number of Subjects Treated						Dose	CAC Tests		
Ref.	Olopatadine				Placebo	Comparator	Per eye	27-min	6-hour	8-hour
	0.01%	0.05%	0.10%	0.15%						
C-94-10	25	24	25	24	Contralat. Eye	None	1 drop	✓	✓	✓
C-94-39		60	60		Contralat. Eye	None	1 drop	✓		✓
C-94-58		30	30		Contralat. Eye	None	1 drop	✓		✓
C-96-15[a]			36		Contralat. Eye	36 Ketorolac 0.5%	2 drops	✓		
C-96-76[c]			66+31[c]		31+32[c] Contralat. Eye	66+32[c] Levocabastine 0.05%	2 drops	✓		✓
C-96-79			20		20	None	2 drops	✓		
C-96-82		30+30[b]			30+30[b]	None	2 drops	✓		✓

27-min, 6-hour, 8-hour = Time of CAC post olopatadine instillation

[a] Crossover study

[b] 30 subjects in each group received olopatadine or placebo only in both eyes, and 30 subjects received 2 drops olopatadine into one eye and 2 drops placebo into the contralateral eye

[c] Three parallel groups, olopatadine/levocabastine, n=66; olopatadine/placebo, n=31; levocabastine/placebo n=32; one treatment in each eye

Dose response

Studies C-94-10, C-94-39, C-94-58 and C-94-80 looked at the dose response of olopatadine in the clinical setting.

Study C-94-10 investigated the onset and duration of action of olopatadine and sought to determine the optimal concentration of olopatadine ophthalmic solution (OOS) for clinical use. This study was a randomised, double-masked placebo-controlled, parallel-group study. 98 male and female volunteers with a history of symptoms of a clinically active allergic conjunctivitis and a positive allergen diagnostic test were enrolled. Two weeks after a confirmatory CAC was performed the action of OOS was assessed by giving one of four concentrations (0.01%, 0.05%, 0.10% or 0.15%) to the volunteers prior to CAC. Giving the drug 8 hours before CAC assessed long-term duration of action and 27 minutes prior to CAC investigated onset of action. Signs and symptoms were then evaluated prior to, 3, 10 and 20 minutes after CAC. All four concentrations of OOS were statistically superior to placebo (dosed in the contralateral eye) inhibiting itching and redness at all post-CAC time points for challenges performed 27 minutes, 6 hours and 8 hours after OOS dosing. Comparisons of the magnitude and maintenance of the response produced by the four concentrations of the solution showed a non-linear dose response. The 0.10% and the 0.05% concentrations appeared to be more effective than the other doses. The difference between the 0.10% and the 0.05% was not statistically significant but at peak challenge times (CAC at 8 hours post olopatadine instillation) the 0.10% concentration produced an overall better result profile. On this evidence the 0.10% dose was chosen as the optimal concentration for clinical usage.

Study C-94-39 was a comparison of the efficacy of 0.05% and 0.10% OOS versus placebo and also investigated the 27 minutes and 8 hours duration of action of olopatadine. 120 male and female volunteers were enrolled in this double-masked, placebo controlled, randomised, contralateral eye comparison study. Both 0.05% and 0.10% concentrations of OOS were statistically and clinically superior to placebo in preventing ocular itching and redness with a clinically significant duration of action for at least 8 hours. Both concentrations of OOS were equally effective in the treatment of allergic conjunctivitis.

Study C-94-58 was similar in design and objective to study C-94-39. A 0.05% and 0.10% OOS were evaluated in 60 healthy male and female volunteers. Both concentrations of OOS were statistically superior to placebo in preventing ocular itching and redness and in inhibiting itching 8 hours after dosing. The two concentrations of OOS were shown to be equally effective in inhibiting redness and itching.

Study C-94-80 was not a CAC study but it is appropriate to discuss it here as it contributes to the evidence for the chosen clinical dose concentration. Study C-94-80 was a Japanese double blind, intergroup, comparative study of efficacy, safety and utility of OOS in patients, aged 6 years or older, with a diagnosis of allergic conjunctivitis (including pollinosis). Concentrations of 0.10%, 0.025% and 0.005% of OOS were used to investigate the optimum effective dose. The primary evaluation parameters included assessing final global improvement taking both changes in subjective symptoms and clinical findings into consideration coupled with evaluating overall safety and utility. Treatment lasted for four weeks. In the evaluation of final global improvement the rates of "moderately improved or better" were 53.7% in the 0.005% group, 55.8% in the 0.025% group and 67.4% in the 0.10% group. No statistically significant differences in the improvement rates were observed among the groups but those treated with the 0.10% concentration of OOS showed the highest improvement rates. In the evaluation of utility the 0.10% group reported the highest rate of 67.4% for "useful or better".

Studies on the proposed dose of 0.1% OOS

Studies C-96-15, C-96-76, C-96-79 and C-96-82 supported the selected dose of OOS 0.10% (OPATANOL) and the proposed indication.

Study C-96-15 (cross-over superiority study) looked at the safety and efficacy of OOS 0.10% in comparison to Ketorolac 0.5% in the treatment of allergen-mediated conjunctivitis induced by ocular allergen challenge in 36 male and female volunteers with a history of symptoms of allergic conjunctivitis. The study concluded that 0.10% of OOS was effective in inhibiting the symptoms of conjunctivitis at all post-CAC time points for challenges performed 27 minutes, and 8 hours after OOS dosing and superior to treatment with ketorolac or placebo. OOS was well tolerated and significantly more comfortable than ketorolac.

Study C-96-76 compared the efficacy of OOS 0.10% versus levocabastine in the treatment of allergen mediated conjunctivitis induced by ocular allergen challenge in 135 adult males and females with a

history of symptoms of clinically active allergic conjunctivitis, a positive allergen diagnostic test and a successful allergen challenge. It was concluded that OOS 0.10% was superior to levocabastine 0.05% or placebo in inhibiting the symptoms of allergic conjunctivitis at all post-CAC time points for challenges performed 27 minutes, and 8 hours after OOS dosing and also that it was safe and well tolerated.

In Study C-96-79, OOS 0.10% was evaluated for efficacy using placebo as a comparator in 40 male and female volunteers with a history of clinically active allergic conjunctivitis. OOS 0.10% was found to be superior to placebo in inhibiting ocular redness, itching and chemosis and was found to be safe and well tolerated.

Study C-96-82 evaluated the efficacy of OOS 0.1% in the treatment of allergen-mediated conjunctivitis induced by ocular allergen challenge in 90 healthy male and female volunteers. OOS 0.10% was found to be superior to placebo in inhibiting ocular itching and redness at all post-CAC time points for challenges performed 27 minutes and 8 hours after OOS dosing, with effects not carried over to the contralateral placebo eye.

- **Other pharmacological studies**

Ocular comfort

Three studies evaluated ocular discomfort. Study C-93-79 looked at the ocular comfort and safety upon instillation of one drop of 0.15%, 0.10%, 0.05% and 0.01% of OOS relative to a marketed product (ketorolac tromethamine 0.50%) in 30 healthy male and female volunteers. Each subject was randomly assigned to one of ten treatment sequences. Subjects received one drop of each concentration of olopatadine and one drop of ketorolac tromethamine 0.50%. At least 24 hours washout period separated the treatments. Immediately following the instillation of each test article subjects completed a 3-minute burning profile and a questionnaire evaluating the comfort of each test solution. The comfort level of the five test solutions was evaluated based on ocular discomfort composite, membrane discomfort composite, visual clarity and burning profile. Adverse events related to all concentrations of OOS were non-serious, mild, usually occurred upon or within one hour of instillation, resolved without treatment and did not interrupt continuation in the study. Ketorolac tromethamine 0.50% ophthalmic solution produced significantly greater ocular discomfort (burning and stinging) than OOS 0.15%, 0.10%, 0.05% or 0.01% and greater membrane discomfort than OOS 0.15%, 0.10% or 0.05%. Ketorolac tromethamine 0.50% also produced a significantly poorer visual clarity profile compared to OOS 0.15%, 0.10% and 0.05%. No significant differences in ocular discomfort were noted between concentrations of olopatadine ophthalmic solutions.

Study C-95-12 and Study C-95-18 evaluated the ocular comfort and safety of OOS as compared to marketed products; Ketorolac tromethamine 0.50% Ophthalmic solution and Levocabastine 0.05% Ophthalmic suspension. Using the same study design and methodology coupled with the same evaluation criteria as Study C-93-79 it was shown in both studies that when administered as a single drop in normal healthy adults OOS 0.1% is significantly more comfortable and produces a less severe burning profile and has significantly less effect on visual clarity than Ketorolac tromethamine 0.50% Ophthalmic solution and Levocabastine 0.05% Ophthalmic suspension. OOS 0.10% produces significantly less membrane discomfort relative to Ketorolac tromethamine 0.50% ophthalmic solution.

Pupil diameter

Topical ocular administration of some antihistamine decongestant combination products have been known to produce pupil dilation as an adverse effect. This mydriatic effect can be produced by either component of the combination. Study C-94-65 looked at the effect of OOS 0.1% versus placebo on pupil diameter one hour following topical administration of one drop in the nondominant eye of normal volunteers. No statistically or clinically significant difference in pupil diameter change from baseline was observed between treatment groups or in either treatment groups.

Tear tryptase level

As current theories suggest that tryptase is released by activated human conjunctival mast cells, by quantifying mast cell activation via tear assays one may be able to evaluate the efficacy of certain pharmacologic agents at the cellular level, e.g. mast-cell stabilising properties. To test this theory an exploratory study (C-95-73) to observe the mast cell stabilising properties of OPATANOL by measuring tear tryptase levels following antigen challenge was performed. But due to technical

problems in the tear sample collection or in the sample handling very low yields of measurable tryptase were obtained. No new conclusions could be drawn from these data.

Thus the membrane stabilising effect of olopatadine that was suggested *in vitro* on human mast cells has not been confirmed.

A study to assess the effect on **QT_c interval** of a twice daily regimen over 2 $^1/_2$ days of dosing with 5mg of oral olopatadine solution compared to placebo oral solution in 100 young and elderly, healthy male and female volunteers was carried out. From Day –2 to Day –1 each subject had a baseline 24-hour ambulatory ECG (Holter) and a serial 12-lead ECG performed. On Day 1 subjects received either of the test solutions every 12 hours for 2 $^1/_2$ days. After a washout period of 5 days the subjects returned to receive the other solution dosed over the same time frame. To investigate any potential effect of olopatadine serial ECGs, 24 hour Holter monitoring, plasma samples and vital sign measurements were taken. It was concluded that olopatadine 5mg BID was safe and well tolerated and was not associated with any effect on QT_c interval and did not prolong QT_c interval relative to placebo.

- ***Summary of pharmacodynamic data***

Seven CAC studies were presented in the clinical programme. Results of the CAC studies confirmed a rapid onset of action and duration of action of at least 8 hours. The selection of a twice daily dosing regimen seems reasonable given the duration of action and that the product will be used during the daytime hours. Based on the positive results of the dose ranging studies the dose of 0.10% of olopatadine was chosen. The efficacy of the chosen concentration of olopatadine was shown in the CAC studies. Olopatadine 0.10% was shown to be significantly superior to placebo and to other marketed ocular products (ketorolac 0.5% and levocabastine 0.05%) in reducing itching and redness. Even if a comparison with placebo would have been more accurate, the ocular comfort studies showed that all concentrations of OOS were well tolerated when instilled and were safe for ocular use as all adverse events related to OOS were non-serious and self-limiting. The membrane stabilising effect of olopatadine on mast cells has not been confirmed.

Pharmacokinetics

Both oral and ocular pharmacokinetic studies have been carried out.

In the pharmacokinetic studies on the oral formulation of olopatadine, blood samples were analysed using a validated radioimmunoassay using ^{3}H-olopatadine and rabbit anti-serum against olopatadine. The method had cross-reactivity against some of the metabolites, but this was considered acceptable as concentrations of these metabolites were low. The limit of quantification was around 0.1-0.2 ng/ml.

The pharmacokinetic studies following topical ocular administration of olopatadine included another bioanalytical method, gas chromatography - mass spectrometry (GC/MS). The lower limit of quantification was 0.5 ng/ml.

The concentrations of olopatadine, the desmethyl metabolite and the N-oxide metabolite in urine were analysed by HPLC.

Pharmacokinetic data were obtained from studies in young and elderly healthy subjects (mainly Caucasian and Japanese) of both sexes. The table below lists the studies investigating the pharmacokinetics of olopatadine. The study population, the number of subjects, the overall design, and the treatments administered in each study are also presented.

Study	Population	Design	Dose regimens (number of subjects)
KW 4679 (1)	Healthy young males	Randomised, double-masked, Placebo-controlled, single-dose, single-centre	Single oral doses of olopatadine 0.5, 1, 2.5, 5, 10, 20, 40, 80, 120, 160, 200, 240, 280, 320, 360 and 400, or placebo (on each dose level, 3 subjects received active drug and 1 received placebo)

KW 4679 (2)	Healthy young males	Randomised, double-masked, placebo-controlled, single-dose and multiple-dose, single-centre	Single oral doses of olopatadine 80 mg or placebo followed by multiple oral doses of olopatadine 80 mg TID or placebo TID for 10 days (12 received active drug and 8 received placebo)
KW 4679 (3)	Healthy young males	Non-randomised, open-label, single-dose, single-centre (Japan)	Single oral doses of olopatadine 5, 10, 20, 40 and 80 mg (6 subjects on each dose level, except 10 mg with 12 subjects)
KW 4679 (4)	Healthy young males	Non-randomised, open-label, single-dose and multiple dose, single-centre (Japan)	Single oral doses of olopatadine 10 mg followed by multiple oral doses of olopatadine 10 mg BID for 6½ days (8 subjects)
C-00-23	Healthy adult males and females	Randomised, double-masked, placebo-controlled, multiple-dose, two-period, crossover, single-centre	Multiple oral doses of olopatadine 5 mg BID for 2½ days and placebo BID for 2½ days (102 subjects)
C-93-75	Healthy adult males and females	Non-randomised, open-label, single-dose, single-centre (USA)	Multiple doses of olopatadine 0.15% BID for 15 days (15 subjects), two drops in each eye
C-93-83	Healthy young males	Non-randomised, open-label, single-dose, single-centre (Japan)	Multiple doses of olopatadine 0.15% BID for 15 days (9 subjects), two drops in each eye
94-314	Healthy young and elderly males	Non-randomised, open-label, single-dose and multiple dose, single-centre (Japan)	Single oral doses of olopatadine 10 mg (6 young subjects and 6 elderly subjects) followed by multiple oral doses of olopatadine 10 mg BID for 6 days (6 elderly subjects)
95-205	Patients with impaired renal function	Non-randomised, open-label, single-dose	Single oral dose of olopatadine 10 mg (six subjects)

- General:

After oral administration peak plasma concentrations are seen 1-2 hours after dosing. Mean C_{max} values range from about 10 ng/ml after an oral dose of 0.5 mg to 7800 ng/ml for the 400 mg dose. No absolute bioavailability study has been reported. Plasma protein binding is about 55-65%. The volume of distribution divided by the extent of bioavailability (V/F) is approximately 200-300 l. Elimination half-life is approximately 8-12 hours. The apparent (oral) clearance is about 16-20 l/h. Olopatadine is metabolised only to a minor degree. Two metabolites have been identified in the urine: N-desmethyl and N-oxide metabolite. About 70% of unchanged olopatadine is excreted in the urine within 48 hours after oral administration of 10 mg olopatadine. With regard to dose-concentration linearity, C_{max} and AUC values appear to increase in a dose-proportional manner in studies. The elimination half-life is moderately higher at steady-state than after single dose. Elderly subjects and patients with impaired renal function have higher (<3-fold) exposure after oral olopatadine than healthy young subjects.

Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totalling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/ml).

Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/ml. The mean elimination half-life in plasma was approximately 8-12 hours and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as parent drug.

- Interaction studies:

No specific drug interaction studies have been presented for olopatadine. As there appears to be low systemic absorption of OPATANOL and as metabolism is a minor elimination pathway with 70% of the unchanged drug eliminated via renal excretion the potential for systemic drug interactions is low. Given the results of lack of activity of olopatadine in human liver microsomes it is unlikely that metabolic interactions through CYP P-450 inhibition would occur or that pharmacological effects are likely to be observed by interaction with drugs causing metabolic blockade.

- Special population:

Renal impairment and elderly: Pharmacokinetic studies with orally administered olopatadine have been conducted in healthy, young and elderly Japanese subjects, and in Japanese patients with renal impairment and those requiring haemodialysis. The findings from these studies, which were conducted with single or twice-daily oral 10 mg doses of olopatadine, showed no clinically relevant differences in the plasma concentrations or urinary recovery of unchanged olopatadine in patients with renal impairment or in the elderly. These findings support that no adjustment of dose is warranted in the elderly or in patients with compromised renal function.

Children: The systemic pharmacokinetics of olopatadine have not been studied in children following either topical or oral administration. The ocular volume of drug distribution in children at age of 3 years and above is similar to that in adults. As a result, the ocular distribution of olopatadine following topical ocular administration of OPATANOL would be similar in adults and children. This estimated peak systemic exposure of olopatadine in paediatric patients ages 3 years and greater following topical doses of olopatadine eye drops is expected to be considerably lower (about 15-fold) than the mean peak plasma concentration obtained in adult subjects (~ 76 ng/ml) who were administered a therapeutic oral regimen of 5 mg twice-daily in study C-00-23. These oral doses were safe and well-tolerated.

Clinical efficacy

Apart from the CAC studies, five studies were performed in Seasonal Allergic Conjunctivitis, four pivotal (one versus cromolyn sodium 2% for six weeks, one versus levocabastine 0.05% for six weeks, and two studies versus placebo for 8 to 14 weeks and for 10 weeks. The fifth study looked at use of olopatadine as adjunctive treatment.

Dose-response studies and main clinical studies

Dose response studies are described in the clinical pharmacodynamic part, the four pivotal trials are described below.

In the pivotal studies, 688 patients were randomised, and 684 were administered active product. Of these 684, 336 were administered olopatadine. All studies were double-masked, randomised (1:1 ratio), parallel group trials. Two of the studies involved also paediatric patients ≥ 4 years of age. An overview over the patient population is given below.

Patient population in the Pivotal Efficacy Studies

Study	*Number of Sites*	*Patients Evaluable ITT Analysis*		*Patients Evaluable PP Analysis*	
		OPATANOL	**Comparator***	**OPATANOL**	**Comparator***
C-00-16 *Vs.* **Placebo**	7 (US)	**64** 26 M / 38 F mean age 38 (range 20-61)	**67** 29 M / 38 F mean age 39 (range 18-87)	**64**	**65**
C-98-37 *Vs.* **Placebo**	5 (US)	**80** 34 M / 46 F mean age 37 (range 17-64)	**79** 31 M / 48 F mean age 38 (range 18-68)	**79**	**77**
C-98-40 *Vs.* **Levocabastine 0.05%**	17 (EU/ AUS)	**101** 44 M / 57 F mean age 36 (range 5-81)	**109** 47 M / 62 F mean age 34 (range 5-70)	**96**	**105**
C-94-61 *Vs.* **Cromolyn sodium 2%**	14 (EU/ AUS)	**91** 51 M / 40 F mean age 33 (range 4-77)	**94** 52 M / 42 F mean age 37 (range 4-75)	**82**	**87**
Total		**336**	**CS** = 94 **LE** = 109 **PL** = 146	**321**	**CS** = 87 **LE** = 105 **PL** = 142

* **CS** = cromolyn sodium 2% **LE** = levocabastine 0.05% **PL** = placebo

EU = Europe **AUS** = Australia **US** = United States

ITT = Intent-to-treat **PP** = Per protocol
M = Male **F** = Female **mean** = mean age in years

The symptom itching and sign redness, were part of the primary endpoints in all 4 trials. However, these endpoints were defined in different ways: in study C-98-37 the primary endpoint was the percentage of visits with patient-assessed scores for itching and redness being zero whereas in the remaining studies ocular redness and itching were assessed by either patient or investigator at different time points.

Two of the studies, C-98-37 and C-00-16 were placebo controlled and were designed not only to demonstrate the efficacy of OPATANOL in treatment of SAC but also in prevention of SAC. Patients were enrolled before or at the beginning of the active pollen season and a CAC challenge was used to confirm ocular allergy at enrolment, though on-going symptoms were not demanded.

Study C-94-61

Patients with a history of allergic conjunctivitis and a positive skin test within the past 12 months to at least one common pollen antigen and with a score of at least 4 on a scale (from none 0 to 4 severe) for ocular itching and 2 for conjunctival hyperaemia in both eyes were randomised to treatment with either olopatadine 0.1% morning and evening and placebo noon and afternoon, or cromolyn sodium 2% four times daily (QID) for 6 weeks.

Patients of child bearing potential were expected to have a negative pregnancy test and to practise contraception and all patients had to avoid certain named concurrent medications.

Efficacy and ocular signs and symptoms were determined at clinic visits at screening and on days 0, 3, 7, 14, 30, and 42. A final visit was performed 2-3 days off therapy.

Daily pollen counts were obtained for most of the common pollens.

Primary efficacy criteria were injection (slit lamp redness scored by use of standard reference photographs) and itching (assessed by the patient). Redness was quantified on a nine-point scale from 0.0-4.0 and itching on a five-point scale 0-4. Secondary efficacy variables were chemosis (slit lamp); eyelid-swelling (slit lamp) scored 0.0 none to 4.0 lid closure, physician's impression (scored 0= clinical cure to 5 = significantly clinically worse) and patients' daily diary for redness and itching for the first and last two weeks of the study (four times a day and scored 0=none to 9= severe).

Primary and secondary efficacy criteria were based on scores for the listed items. Repeated measures analysis of variance was used for treatment comparisons and interval estimation for the primary and secondary efficacy parameters. With 86 patients per treatment group, it was considered that the study had greater than 80% coverage probability that a 95% confidence interval would fall within plus or minus 0.5 units for itching and redness score. Olopatadine was therefore to be declared *non inferior* (equivalent) to cromolyn if the upper 95% confidence interval of the mean difference between treatments in ocular itching and redness was less than plus 0.5 units. The plus 0.5 unit was selected because it represented one half of the smallest increment on the itching scale and the smallest increment on the redness scale. The following was listed as an analysis clarification: if two sided 95% confidence intervals for the treatment difference between olopatadine and cromolyn were to lie entirely below zero then it is suggested that it is acceptable to calculate the probability associated with a test of superiority.

Results

For the tests of non-inferiority, the PP data set was used. Wherever the upper 95% confidence limits lay entirely below zero, the ITT data set was used to obtain probabilities associated with two-sided tests of superiority.

Using per protocol data, for itching and redness differences, the upper 95% confidence limits at all visits were less than +0.5 units suggesting that olopatadine was non-inferior to cromolyn.

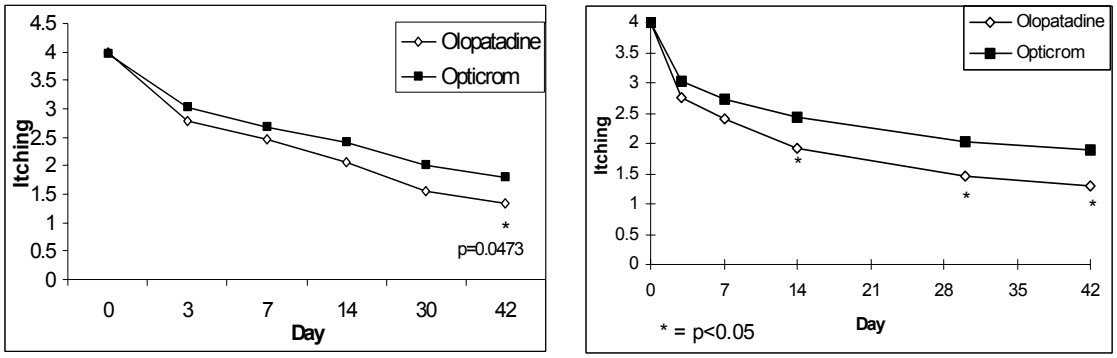
Because the upper confidence limit lay below 0 for 3 of 5 points for ocular itching and 1 of 5 for ocular redness, it was considered that this represented evidence of superiority for olopatadine. The observed upper 95% confidence limit for the difference between treatments was less than zero (much less than 0.5 unit) for itching by day 14 and redness by day 42.

Per protocol analyses showed statistically significant differences in favour of olopatadine on itching for days 14, 30 and 42.

Intent to treat data was significant only at day 42 and the differences between the intent to treat and per protocol analyses is thought to have been due to 9 patients who were excluded (6 in the olopatadine group and 3 in the cromolyn group) because of unproven allergic status at the time of entry.

C-94-61: Mean Ocular Itching Score by Treatment

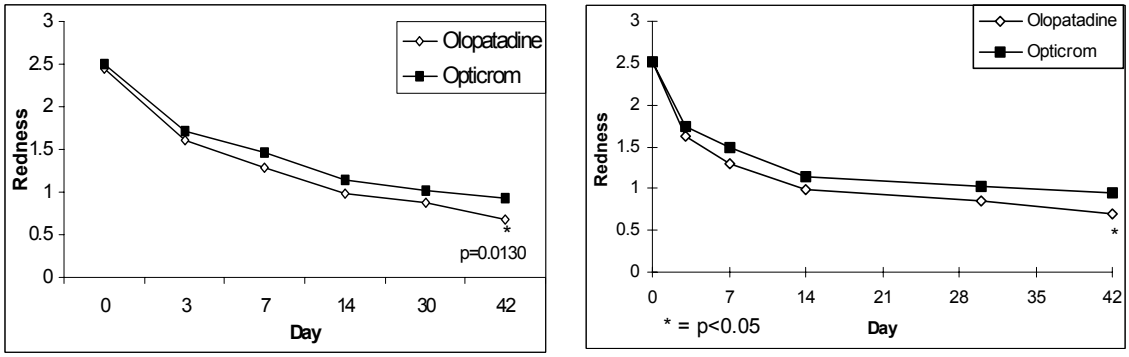
Intent-to-Treat **Per Protocol**



Opticrom = cromolyn sodium 2% **Olopatadine** = OPATANOL

C-94-61: Mean Ocular Redness Score by Treatment

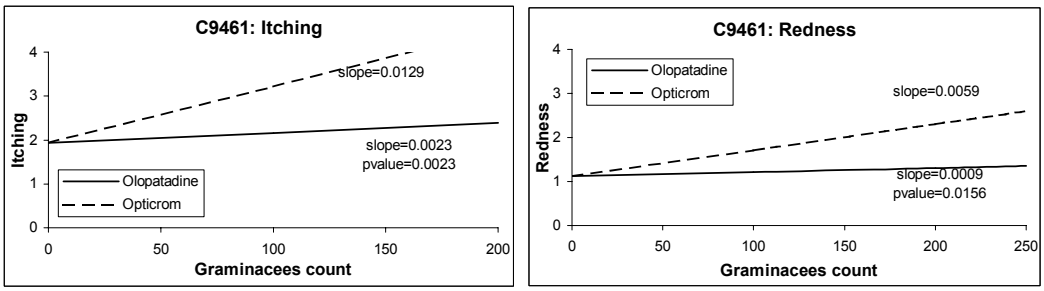
Intent-to-Treat **Per Protocol**



Opticrom = cromolyn sodium 2% **Olopatadine** = OPATANOL

Exploratory analyses were performed to assess impact of pollen levels on the efficacy variables and pollen levels were checked every day. As graminacees were the most common pollen type (in 115 of 185 patients at baseline) and as the study was performed in the active period of graminacees, these levels were chosen for the analysis. Olopatadine relative to cromolyn statistically significantly reduced the effect of graminacees on both itching and redness. The slopes of the lines predicting ocular itching and redness from the graminacees counts for olopatadine were more than five times lower than the slopes for cromolyn.

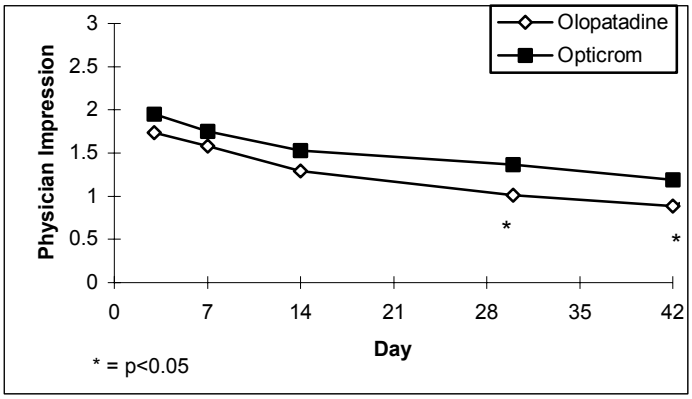
C-94-61: Correlation between Itching and Redness, and Pollen Counts (Intent-to-Treat)



Opticrom **= *cromolyn sodium 2%*** *Olopatadine* **= *OPATANOL***

With regard to *secondary efficacy criteria,* according to physician's impression Olopatadine was superior to cromolyn on day 30 and 42 in the per protocol analysis. Intent to treat showed marginal non-significance in alleviating ocular signs and symptoms on days 30 and 42. There were no differences for chemosis and eyelid swelling.

C-94-61: Physician's Impression by Treatment (Per Protocol)



Opticrom = cromolyn sodium 2% **Olopatadine** = OPATANOL

In the patient diary a visual analogue scale was used to score itching and redness from 0 (none) to 9 (severe) four times a day for the first 15 days and from days 30 to 42 of the study. Maximum scores were used for the analysis. There were no significant differences in the intent to treat data for peak itching or peak redness although there was a suggestion in favour of Olopatadine in the per protocol analysis.

Olopatadine was noted to produce immediate relief from itching and redness with a clinically significant reduction from baseline within 30 minutes and this reduction progressed over four hours. By four hours, olopatadine had caused a reduction in itching and redness in 38%, while reductions were noted for cromolyn in 37% for itching and 26% for redness.

In summary, olopatadine was not inferior/superior to cromolyn in alleviating ocular itching and redness, and physicians rated olopatadine superior to cromolyn by day 30. The exploratory analysis relating pollen levels and allergic response offered supportive evidence that olopatadine significantly reduced the effect of pollen on itching relative to cromolyn sodium.

Study C98-40

This study was comparing efficacy and safety in patients over 4 years of age with moderate to severe SAC. Levocabastine is noted to be highly selective second-generation histamine H1 receptor antagonist which is on the market in several countries in the European Union.

Patients with a history of allergic conjunctivitis for at least one allergy season and a positive skin test within the past 12 months to at least one common pollen antigen and with a score of at least 4 on a scale (from 0 none to 5 continuously) for ocular itching and 2 (on a 9-point scale from 0-4) for conjunctival hyperaemia (slit lamp) in both eyes were randomised to treatment for 6 weeks.

Products were administered "in the morning and in the evening".

Efficacy and ocular signs and symptoms were determined at clinic visits on days 0, 7, 14, 30, and 42. A final visit was performed 2-3 days off therapy.

The primary objective of the study was to demonstrate the superiority of olopatadine over levocabastine in reducing ocular itching and injection (slit lamp redness). Primary efficacy criteria were injection (slit lamp redness assessed by the investigator) and itching assessed by the patient during the visit. Itching was graded on a 0-5 scale (0= none and 5=continuously) and slit lamp redness was graded on a nine point 0.0-4.0 scale (0=none and 4=severe).

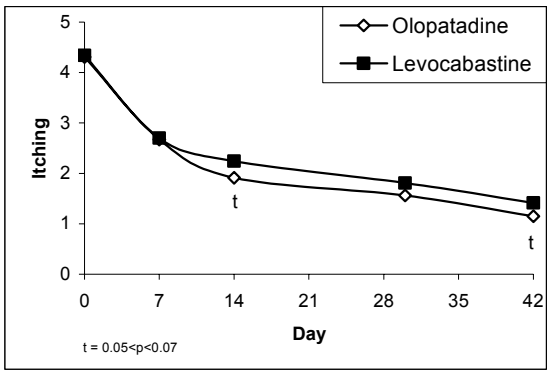
Secondary efficacy variables were redness (self assessed by the patient), chemosis, eyelid swelling, nasal signs and symptoms, physician's impression and patient's diary for redness and itching. From a safety point of view, visual acuity and pupil diameter were recorded at every visit and intraocular pressure and undilated fundus examination were performed at beginning and end of the study.

Results

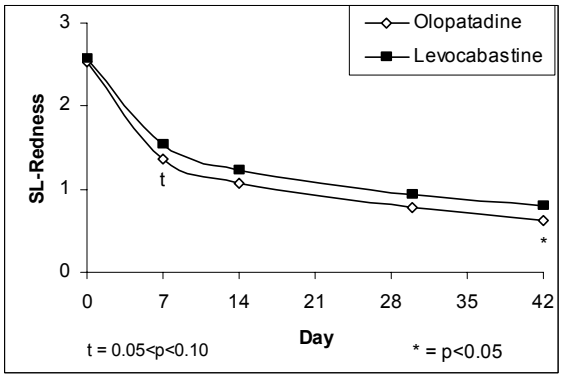
Primary efficacy criteria: the study did not suggest that olopatadine was superior to levocabastine. Using intent to treat data, olopatadine was superior to levocabastine with regard to slit lamp redness only on day 42, although this became non significant after adjustment for multiplicity. Olopatadine was marginally non significant for itching on days 14 and 42. Otherwise there were no statistically significant differences between the two treatments. Differences noted in the intent to treat analysis were not significant in the per protocol data set. The main factor causing the difference was thought to relate to whether patients discontinued prematurely.

C-98-40: Mean Ocular Itching and Slit-lamp Redness Score by Treatment (Intent-to-Treat)

Itching



Slit-lamp Redness



Olopatadine = OPATANOL

Regarding secondary efficacy criteria, according to Physician's impression (recorded on a 6-unit scale ranging from 0-cure to 5-worse), olopatadine was superior to levocabastine on day 14, 30, and 42 in the intent to treat analysis and this was maintained after adjustment for multiplicity. Chemosis and eyelid swelling were evaluated on a 5-unit scale from 0 (none) to 4 (severe). Redness was self evaluated by the patient (0=none and 5=continuously). Using intent to treat data, olopatadine was statistically superior to levocabastine for chemosis at all visit points, eyelid swelling (7, 14 and 42) and self assessment of redness on day 42. In the patient diary a visual analogue scale was used to score itching and redness from 0 (none) to 9 (severe) daily before the evening dose for the duration of the study. Maximum scores were used for the analysis. In the intent to treat data there were significant differences in favour of Olopatadine on days 14 and 30 for itch. There were no significant differences regarding redness. Nasal signs and symptoms were included as secondary efficacy variables with nasal stuffiness, sneezing, runny nose, itchy nose, and postnasal drip evaluated on a 6-unit scale (0=none and 5=continuously). Both Olopatadine and levocabastine produced significant reductions from baseline for stuffy nose, sneezing, runny nose and itchy nose at each follow up visit. Olopatadine had a consistent effect on nasal drip but levocabastine had an effect only at day 30 and 42. Results for per protocol and intent to treat were similar.

Pollen data were analysed for graminacees which was selected for 15 of the 17 sites and the pollen type to which 185 patients were allergic. Results suggested no difference between Olopatadine and levocabastine.

In summary, using intent to treat data, olopatadine twice daily (BID) was superior to levocabastine BID in alleviating ocular redness (slit lamp) by day 42 only. Itching was marginally better by day 42. Overall, the trial failed to show that olopatadine was superior to levocabastine.

Study C98-37

This study was assessing efficacy of olopatadine (1 drop BD at an interval of 6 to 8 hours) in prevention and relief of signs and symptoms in patients with allergic conjunctivitis, versus placebo (vehicle). Adult patients with a history of SAC and a positive skin prick test with ragweed antigen within the last two years (and a positive bilateral conjunctival antigen CAC test to ragweed at baseline) were administered olopatadine or placebo (vehicle) for at least 8 weeks, until first killing frost or ragweed pollen counts of zero.

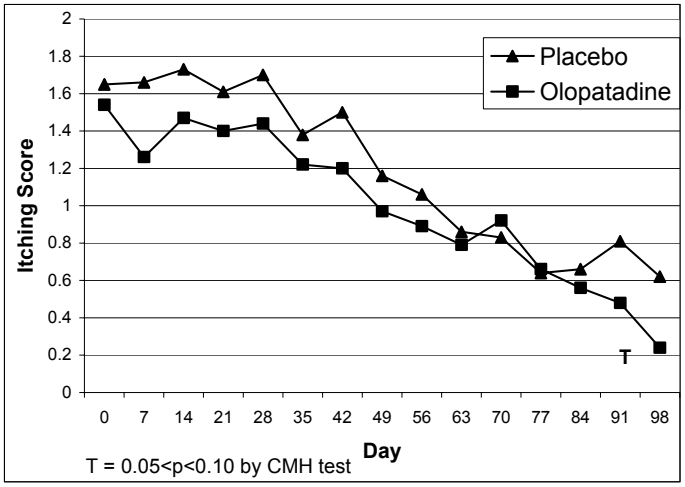
Patients were evaluated at screening and on days 7, 14, 28, 42, 56, 70, 84, and 98. Patients were asked using a scale (0=none to 4= very frequently) how often in the previous days had their eyes itched or were more red than normal. Primary efficacy criterion was percent of visits with ocular itching and redness scores= zero (patient's assessment). For each patient a score was calculated that was the percentage of that patient's evaluable visits when itching and redness were concurrently zero. Secondary efficacy variables were percent of visits with zero scores for individual ocular signs and symptoms of itching, redness, tearing, slit lamp redness, chemosis and eyelid swelling; mean scores for individual ocular signs and symptoms averaged over three consecutive weeks when pollen counts were maximal at the site; percent of visits with zero scores for individual nasal signs and symptoms. From a safety point of view, visual acuity, intraocular pressure and undilated fundus examination were performed at beginning and end of the study.

Results

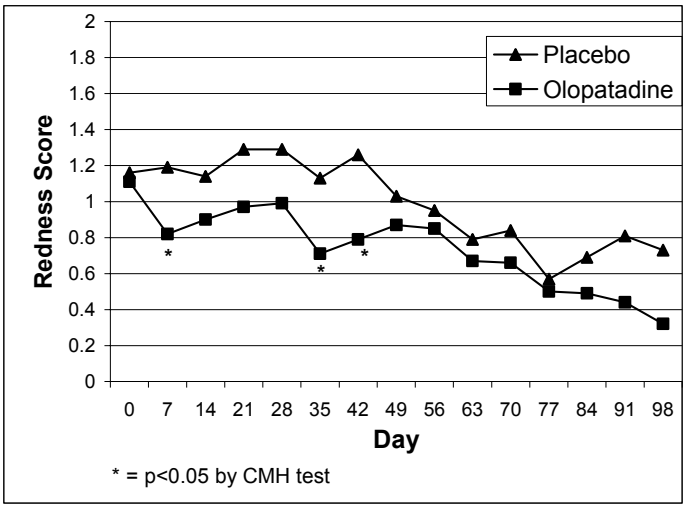
The statistical objective was to show superiority of olopatadine over placebo in the prevention of itching and redness. All efficacy analyses used only data from the active ragweed season. The secondary analysis that compared average scores for signs and symptoms of allergic conjunctivitis used only data from the three-week peak pollen season at the site.

Although olopatadine consistently reduced signs and symptoms of allergic conjunctivitis and allergic rhino conjunctivitis compared to placebo, the results did not gain statistical significance in the study primary and secondary analyses. It is suggested that the poor results were related to the low ragweed pollen counts at one site where 42% of this study were enrolled.

C-98-37: Mean Itching Scores by Visit Day (Intent-to-treat)



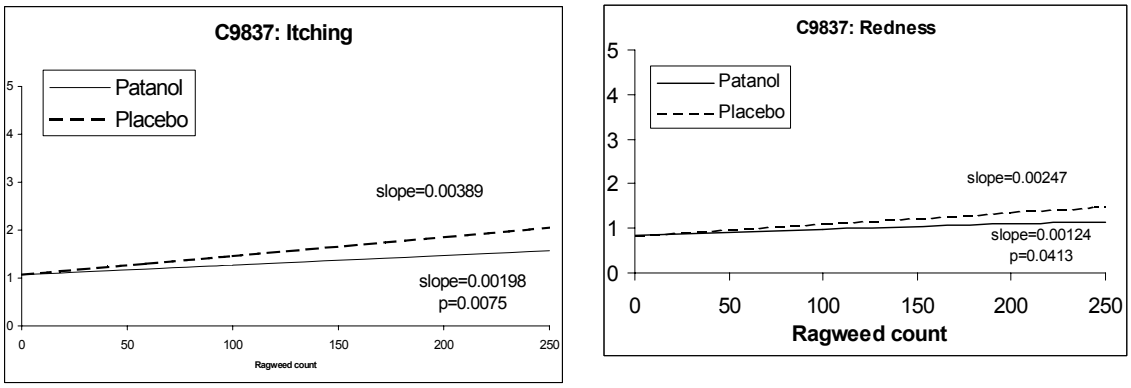
C-98-37: Mean Redness Scores by Visit Day (Intent-to-treat)



There were no statistically significant differences in the number of patients free of concurrent itching and redness between the olopatadine and placebo groups although percentages were slightly higher in the olopatadine group. Results for individual ocular signs and symptoms scores were similar. Mean scores for both itching and redness decreased for both Olopatadine and placebo over the period of the study. Pollen levels were variable and the lowest counts were seen at a site, which had recruited 42% of the patients. Because of this finding, exploratory analyses were performed on all patients and all study visits and based on the correlation between efficacy parameters and pollen counts. Excluding data from this site did not produce statistically significant differences for the primary efficacy variable but did suggest that olopatadine produced a significant improvement in concurrent itching and redness over the three-week peak pollen season. The percentage of visits when patients were free of ocular redness and slit lamp redness during active pollen season was marginally greater for olopatadine than placebo.

C-98-37: Correlation between Itching and Redness and Pollen Counts

Itching **Redness**



There appeared to be a significant correlation between pollen levels and signs and symptoms of allergic conjunctivitis and slopes of pollen counts against ocular itching, redness and tearing were two to three times lower with olopatadine than with placebo. Olopatadine effects were greatest when pollen counts were medium or high. For slit lamp redness, slopes were not significant. Similarly, for chemosis and eyelid swelling there were no significant differences between the slopes. The applicant suggested that the lack of correlation for these variables could be explained by the fact that patients

drive to the doctor's office and so remove themselves from their usual environment to an environment containing low levels of allergen in the clinic.

Olopatadine produced a significant increase in the percent of visits with runny nose scores of zero and a marginally significant effect in the runny nose average score during the 3-week peak pollen season.

In summary, results were not statistically significant for the planned primary or secondary analyses. Olopatadine failed to demonstrate superiority to placebo in prevention of redness and itching as documented by the percent of visits with a zero score for both redness and itching. The post-hoc exploratory analysis appeared to suggest a significant correlation between pollen levels and signs and symptoms of allergic conjunctivitis as slopes of pollen counts against ocular itching, redness and tearing were two to three times lower with olopatadine than with placebo.

Study C00-16

This study compared olopatadine and placebo (Opti-Tears II- an OTC artificial tear preparation) in the prevention and relief of signs and symptoms of allergic conjunctivitis and rhino-conjunctivitis. This study was performed to confirm the results of C98-37 in which a post hoc analysis correlated pollen and signs and symptoms of allergic rhino-conjunctivitis.

Adult patients with a history of SAC and a positive skin prick test with grass pollen allergen within the last two years and a positive bilateral CAC test of the required magnitude to grass allergen at baseline were administered olopatadine or placebo to each eye daily morning and evening for 10 weeks. Pollen counts were obtained over the entire treatment period. Patients were evaluated at screening and once a week for 10 weeks during the study. Assessments alternated between telephone and in patient visits and patients were asked using a scale (0=none to5=continuously) how often in the previous days had their eyes itched or were more red than normal.

Primary efficacy parameters were patient self-assessments scored on a 6-unit scale of the frequency of ocular itching and ocular redness during the three days before each evaluation (0=none and 5= continuously). Repeated measures analysis of variance was used to compare treatment differences in the slopes for ocular itching and redness as a function of grass pollen counts.

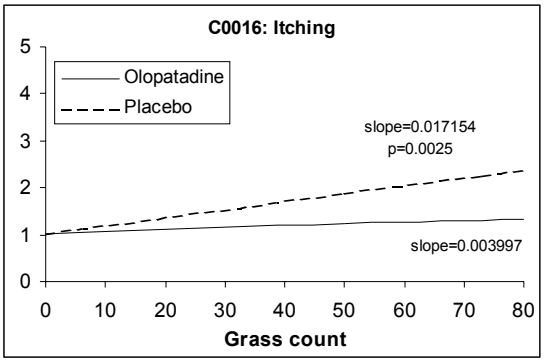
Secondary efficacy variables included scores for slit lamp total redness (0=none and 4=extremely severe); chemosis, slit lamp (0=none to 4=severe); eyelid swelling, slit lamp (0=none to 4= lid closure) and tearing, patient self assessment (0=none to 5=continuously). In addition, scores (0=none to 5=continuously) were collected for itchy nose, stuffy nose, runny nose, postnasal drip and sneezing. Repeated measures analysis of variance was used to compare treatment differences in the slopes for secondary efficacy parameters as a function of grass pollen counts. From a safety point of view, visual acuity, intraocular pressure and undilated fundus examination were performed at the beginning and end of the study.

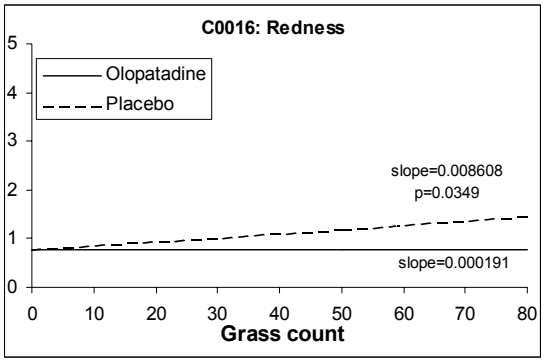
Results

Olopatadine significantly reduced the effects of pollen counts on ocular itching and redness relative to placebo; slopes of lines predicting ocular itching and redness from pollen counts for the olopatadine group were significantly lower than the slopes with placebo. Results of per protocol and intent to treat data sets were similar. Mean scores for itching and redness were consistently lower in the Olopatadine group compared to placebo for all assessment time points. There were significant difference for itching on days 7, 14, 35, 63, and 70. There were significant differences for redness on days 14, 28, 42, and 63.

C-00-16: Correlation between Itching and Redness and Pollen Count (Intent-to-treat)

Itching **Redness**





No significant differences were noted in scores for slit lamp redness, chemosis, or eyelid swelling. Olopatadine did reduce the effect of pollen counts on tearing (marginally non-significant). Olopatadine significantly reduced the effects of pollen on sneezing, runny nose, and itchy nose relative to placebo. The slopes relating sneezing, runny nose, and itchy nose to pollen counts were lower for olopatadine than for placebo but there were no significant differences between them for postnasal drip and stuffy nose.

In summary, olopatadine, using a planned slopes analysis to show the correlation between pollen counts and symptoms, was superior to placebo in reducing ocular redness and itching. There were significant difference between olopatadine and placebo for itching on days 7, 14, 35, 63, and 70 and for redness on days 14, 28, 42, and 63, but no differences for slit lamp redness, chemosis, or eyelid swelling.

Supportive study

Study C98-04 was a multicentre, randomised, observer masked, parallel group, in which patients were randomised to receive either loratadine 10mg once daily or loratadine once daily plus one drop of olopatadine into each eye twice daily for 7 days. This study sought to compare the effect of olopatadine use with loratadine to loratadine alone on ocular signs and symptoms in patients (at least 6 years of age) with moderate to severe SAC.

94 patients were enrolled but 10 did not meet inclusion exclusion criteria and 6 patients were discontinued from each group. 45 patients received loratadine and olopatadine and 49 received loratadine alone. Patients recruited had a history of SAC and a positive skin test within the last two years and a score of 4 (scale 0-4) for ocular itching and 2 or more (scale 0-4) for conjunctiva on day 0.

Primary efficacy parameters were ocular itching and redness. Patients scored ocular itching at each visit (scale 0-4). The investigator scored redness at clinic visits (scale 0-4) on days 0, 3 & 7.

Patients scored nasal signs and symptoms such as stuffy nose, sneezing, runny nose, itchy nose and postnasal drip (scale 0-4). Physician's global assessment of ocular and nasal conditions was on a scale of 0-5 (clinical cure to significantly clinically worse). Patient's diary assessment (4 times per day) of ocular itching and redness scored 0-9 (none to severe). Quality of life questionnaires consisted of 28 items from 7 domain areas.

The primary parameter conjunctival redness, assessed by the investigator, did not show any treatment differences, the differences for the primary parameter itching, assessed in-office, was significant at study end whereas apart from nasal symptoms, all patient assessed parameters showed an advantage for the OPATANOL adjunctive group. It should be noted that it was single-masked (investigator) study, therefore, patients may have biased in their evaluation of the efficacy parameters.

Discussion on clinical efficacy

Apart from the evidence provided by the CAC studies, the pivotal efficacy studies were performed comparing olopatadine with levocabastine (six weeks treatment), cromolyn sodium (six weeks treatment), and placebo (eight to fourteen weeks treatment).

The study with cromolyn showed that for slip lamp redness and itching, olopatadine was non inferior. Results for secondary efficacy criteria showed no difference for chemosis or eyelid swelling and physician's impression suggested superiority on days 30 and 42 only.

The study with levocabastine, which used the standard lower dose of levocabastine that is usually prescribed, showed superiority for slit lamp redness or itching only on day 42. For secondary end points olopatadine was superior in controlling ocular swelling and chemosis.

The first study with placebo had fairly difficult criteria to meet in order to be significant but the study failed to meet either primary or secondary efficacy criteria. Even with the exploratory analysis relating pollen levels to signs and symptoms, results were not always significant. Although placebo is known to be associated with some clinical improvement it was surprising to see the degree of progressive improvement that appeared to occur with placebo administration.

A second study using placebo and performing the slope analysis suggested that olopatadine was superior to placebo for patient assessment of ocular itching and redness but was negative for investigator assessment of slit lamp redness or chemosis.

The concept of the slope analysis (relationship between pollen count and allergic response) and the differences between subjective and objective measurements were therefore questioned for supporting the efficacy of olopatadine.

With regard to nasal signs and symptoms, these were secondary end points in the two placebo studies and in the study using levocabastine as comparator. Overall, the results were inconsistent, but data suggested that Opatanol may reduce the nasal signs and symptoms in patients with patent nasolacrimal ducts.

Clinical safety

Patient exposure

In the development of olopatadine there were 2587 subjects or patients who were enrolled in 28 trials. 16 of the 28 clinical trials were in normal subjects. The total number who received olopatadine whether alone or in association with any other drug was 1415 of whom 710 were normal subjects and 705 were allergy patients.

Duration of exposure ranged from 1 to 184 days.

Of the 705 patients, 246 were administered one to two drops bid in one or both eyes, 429 one drop bid daily in both eyes, and 30 patients one to two drops QID in one or both eyes.

Eight of the 16 clinical studies were conducted in patients with a history of clinically active allergic conjunctivitis who underwent a CAC.

268 of the subjects were between 3 and 17 years.

Two studies were performed to specifically address safety of olopatadine.

In **C-94-52**, olopatadine was administered to 369 volunteers three times per day (TID) for 42 days. Ages ranged from 3 to 79 years. Patients were randomised to drug or placebo in this double-masked parallel group study in asymptomatic subjects. Safety measures included intraocular pressure, pulse, systolic and diastolic blood pressure, and visual acuity. No clinically significant changes in visual acuity, ocular signs, dilated fundus, intraocular pressure, pulse or mean arterial pressure were seen in either group. Ninety of the 244 subjects (36.9%) receiving olopatadine experienced adverse events compared to 44/125 (35.2%) given placebo. Four of the 23 (17.4%) olopatadine patients aged 3-6 and four of the 13 placebo patients (30.8%) experienced adverse events. Overall the study suggested that topical dosing with olopatadine 0.1% (OPATANOL) administered three times (TID) a day for up to 42 days was safe both in the 55 subjects who were under 17 years (23, 3-6 years, and 32, 7-16 years) and in the 189 subjects over 17 years.

The second study performed to assess safety, C96-81 was a single centre, double masked, parallel group, randomised, active control study to examine corneal safety following administration of olopatadine 0.1% (OPATANOL) or cromolyn sodium 4% ophthalmic solution in patients with vernal keratoconjunctivitis, administered 1 drop QID at 4-6 hourly intervals for 90 days. The object was to estimate the difference in effects on corneal thickness endothelium cell density and morphology. There were 30 patients in each group. Mean age was 9.63 years in this group and the range was 5 to 17 years. Safety was based on the extent of exposure to study drug, visual acuity, ocular signs and symptoms, corneal thickness (using pachymetry), and density (using specular microscopy) and adverse events. There were no statistically or clinically significant changes from baseline for pachymetry (corneal thickness) or corneal cell density. Adverse events were mild to moderate and there were no serious adverse events recorded in this study. There were no clinically or statistically significant changes in visual acuity.

Adverse events and serious adverse event/deaths

The overall rate of adverse events with olopatadine monotherapy was 21.5% compared to 31.2% in the placebo group. The most common overall (treatment related and unrelated) adverse events were ocular discomfort and headache.

Events related to therapy: The most common ocular event related to olopatadine was ocular discomfort (burning or stinging). Ocular pruritus, ocular hyperaemia, ocular discharge and keratitis were also associated. The most common non-ocular events were headache, asthenia, dry nose and taste perversion.

Events not related to therapy: The most frequent ocular events were keratitis and ocular hyperaemia.

The most frequent non-ocular events were headache, cold syndrome, and rhinitis. Severe headache, cold syndrome, infection, surgical/medical procedure, abdominal pain, migraine, diarrhoea, gastrointestinal disorder, convulsion, drug dependency with addiction, asthma, bronchitis, pneumonia, pneumothorax, laryngismus and pleural disorder were reported in a total of 15 patients.

In the *main clinical studies* (CAC and environmental studies) involving approximately 950 patients, the following undesirable effects were determined to be definitely, probably or possibly related to treatment:

- *Ocular Effects:* ocular discomfort (0.9%), ocular pruritus (0.6%), ocular hyperaemia (0.4%), ocular discharge (0.4%), keratitis (0.4%), dry eye (0.3%), lid oedema (0.2%), foreign body sensation (0.2%), photophobia (0.2%).
- *Systemic Effects:* Headache (0.4%), asthenia (0.3%), dry nose (0.3%), dizziness (0.2%).

The incidence of all undesirable effects was uncommon.

Deaths and Serious Adverse Events: No deaths occurred during the trials. Three patients experienced serious non-ocular adverse events unrelated to olopatadine(surgical/medical procedure, pneumothorax, bronchitis, convulsion, pleural disorder, pneumonia, drug dependency with addiction, gastrointestinal disorder).

In post-marketing experiences with olopatadine, the following additional undesirable effects have been very rarely (<0.01%) reported: blurred vision, dry mouth, rhinitis, and erythema. They are generally accepted as related to the use of antiallergic/antihistaminic agents.

Discontinuation due to adverse events

The overall rate of discontinuation due to an adverse event while on treatment with olopatadine was 1.7% and the rate of treatment related discontinuation due to olopatadine was 0.5%.

Six subjects were discontinued because of ocular events (ocular discomfort, ocular pruritus, epitheliopathy, keratitis, ocular pain, ocular discharge, and corneal erosion). Three subjects were discontinued due to non-ocular events (contact dermatitis, dizziness, hypoesthesia, and headache).

Eleven subjects discontinued due to ocular events not considered related to therapy; conjunctivitis, keratoconjunctivitis, corneal ulcer, chalazion, increased ocular pressure, pigment dispersion syndrome, foreign body sensation, ocular oedema, hordeolum, corneal abrasion, ocular discharge, ocular

haemorrhage, blepharitis, surgical/medical procedure or ocular hyperaemia. Five subjects discontinued due to allergy, asthma, cold syndrome, dermatitis, sinusitis, or bronchitis.

Laboratory findings

Laboratory values were evaluated in 2 clinical studies (C-93-75 and C-93-83) with topical ophthalmic olopatadine and in one clinical study (C-00-23) where the effect of oral olopatadine was investigated. No clinically significant changes were noted for blood chemistry, haematology, or urinary analysis values.

Cardiovascular parameters were measured in four clinical studies. Pulse and blood pressure were evaluated in 3 clinical studies, no significant changes were observed. No clinically significant trend toward QT prolongation was associated with oral administration of Olopatadine 5 mg twice daily (BID) in 1 clinical study.

Visual acuity was measured in 21 clinical studies. A clinically significant decrease of visual acuity, expressed as a decrease of ≥3 Snellen lines, was observed in 6 subjects out of 988 receiving olopatadine 0.1% (0.6%) and in 2 subjects out of 336 receiving placebo (0.6%).

Intraocular pressure was measured in 14 studies. A clinically significant increase in IOP was defined as an increase of ≥10 mmHg and was observed in 1 subject receiving olopatadine and in 2 subjects receiving placebo.

Pupil diameter was measured in 7 clinical studies in 710 subjects using a standardised graduated (0.5mm increments) pupil diameter scale. No significant changes were noted for any of the applied treatments.

Pupillary response was evaluated in 24 subjects receiving olopatadine 0.15%. Abnormalities were not observed.

Ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber) for changes unrelated to the efficacy measurements were recorded in 12 clinical studies involving 1268 subjects; the incidence of an increase in these ocular signs was not higher than in the placebo group.

Fundus examinations were performed in 11 clinical studies and changes in fundus parameters were reported as adverse events. Retinal degeneration unrelated to olopatadine was noted in one patient, otherwise, no significant changes in fundus parameters were noted.

Corneal thickness was measured in study C-96-81 (see above).

Safety in special populations

A breakdown by age of adverse events following olopatadine, comparator groups and placebo was provided. The age categories include children (3 to 11 years of age), adolescents (12 to 17 years of age), adults (18 to 64 years of age) and the elderly (≥ 65 years of age).

A review of this information suggests that children in the age range of 3 to 17 years experienced more ocular adverse events (i.e., keratitis) compared to the older age groups (≥ 18 years of age) following treatment with olopatadine. Keratitis, fever, rhinitis were adverse events with a notable difference in the incidence for children and adults (keratitis incidence 4.3% in children vs. 0.5% in adults and 2.3% in elderly, fever incidence 2.2% in children vs. 1.2% in adolescents and 0.2% in adults and rhinitis incidence 3.2% in children vs.1.8% in adults). Most of the paediatric cases of keratitis occurred in vernal keratoconjunctivitis (VKC), which is a more serious disease than SAC predominantly affecting children. If the patients with VKC are not included, the overall incidences of keratitis in non-VKC patients are similar comparing children (3 to 17 years of age; 2/269, 0.8% incidence) and older patients (≥ 18 years of age; 5/1033, 0.5% incidence). An exclusion of these keratitis cases when comparing incidences between the different age groups seems justified.

There was no age related patterns in the incidence of other ocular and all non-ocular adverse events.

Discussion on clinical safety

Olopatadine administered one to four times daily for up to 120 days or more as monotherapy, adjunctive therapy or by eye treatment was safe and well tolerated in both normal subjects and patients. Adverse

events were for the most part mild to moderate, and usually resolved without treatment. The most common ocular adverse events were ocular discomfort (burning and stinging).

Overall keratitis was reported as an adverse event in 14 of the 1415 subjects/patients (1.0%) receiving olopatadine and in 3 of the 385 subjects/patients receiving placebo (0.8%). Keratitis was reported as being related to olopatadine in 4 of the 14 patients (0.3%) and was characterised as non-serious and mild to moderate, occurred within the first 15 days of therapy, usually resolved with or without therapy and generally did not interrupt patient continuation in the study. Keratitis was reported as being unrelated to olopatadine in 10 of the 14 patients (0.7%). The unrelated cases were attributed to the illness being treated (allergic conjunctivitis or vernal keratoconjunctivitis), intercurrent illness (meibomitis, conjunctivitis, upper respiratory infection), idiosyncratic effect, or ocular irritation from rubbing of the eye(s). Finally, there have been three spontaneous reports of keratitis based upon a review of the post-marketing experience with olopatadine for the period from January 1, 1997 to December 31, 2000. This translates into a very low incidence of 0.000036% based upon the 8.3 million units that were sold during this time period. Therefore, keratitis was not considered a major safety issue.

Safety profiles were similar among children, adolescent, adult and elderly patients. There were no clinically significant different changes from baseline in visual acuity, intraocular pressure, pupil diameter, ocular signs, or fundus parameters between olopatadine or any of the comparators. There were no clinically significant changes from baseline in corneal thickness or endothelial cell density observed over a three-month period. There were no clinically significant changes from baseline in pulse or blood pressure noted in patients receiving olopatadine. There were no clinically significant trends toward QTc prolongation found to be associated with olopatadine 5mg twice times daily (BID).

The safety profile of olopatadine is acceptable particularly in the context of drug type and the small dose required for topical administration.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The important quality characteristics of the active substance are well-defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic of a solution for ophthalmic use. The specifications and batch analytical results indicate a consistent product with a uniform clinical performance from batch to batch. There are no outstanding quality issues which have a negative impact on the benefit/risk balance.

At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that olopatadine has high *in vitro* affinity for the histamine H_1 receptor and suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. Olopatadine significantly reduced the allergic response in *in vivo* conjunctival and classical systemic models of allergic conjunctivitis. The general pharmacology studies showed that secondary pharmacodynamic effects, including those on the cardiovascular system, are possible at doses and exposures well in excess of those anticipated following topical ocular administration in man.

From the pharmacokinetic point of view, oral and topical pharmacokinetics were similar in all relevant species. Absorption, distribution and elimination are rapid and biphasic. Exposure appears to be dose proportional to a threshold level that exceeds likely clinically relevant levels in all species. The role of cytochrome P450 enzymes in olopatadine HCl metabolism has not been elucidated fully. Elimination is mainly in the urine and bile.

Overall, the toxicology programme revealed no special hazard for humans.

Efficacy

Olopatadine appears to have similar efficacy to that of either cromolyn sodium or levocabastine in the treatment of symptoms of seasonal allergic conjunctivitis. However the placebo-controlled studies failed to show superiority of olopatadine in one case and showed clinically significant evidence of superiority in the second where the slope analysis attempted to relate signs and symptoms to pollen levels.

Explanations were requested on the slope analysis and the hypothesis that the relationship (slope) between pollen and allergic response is different for drug and placebo, and the clinical significance of difference between these slopes.

In Seasonal Allergic Conjunctivitis (SAC), signs and symptoms are a series of relatively short-lived events and depend upon environmental conditions (mainly pollen levels).

In the slope analysis, it is assumed that the amount of pollen in the atmosphere is roughly predictive of the exposure of a group of patients to pollen and that atmospheric pollen is predictive of the manifestation of allergic response for the group of patients. The slopes analysis aligns the data (signs and symptoms) based upon pollen level rather than time on study (as in classical analysis of clinical trial results). This analysis was employed in the two placebo-controlled trials (C-98-37 and C-00-16), and was exploratory in C-98-37 but was declared as the primary efficacy analysis in C-00-16. The slopes analysis used in these studies tests whether the treatment controls allergic response to pollen in the environment. Specifically, the slopes analysis tests the hypothesis that the relationship (i.e., slope) between pollen and allergic response is different for drug and placebo. The test of homogeneity of slope recognises that there is no expected difference between treatments when pollen levels are low but that there are expected treatment differences when pollen levels are high. Under this test (slopes analysis), a placebo or ineffective drug would have a positive slope indicating that signs and symptoms increase when pollen increases. On the other hand, a perfect drug would have a slope of zero indicating that when pollen levels are high, patients would be predicted to have no more signs and symptoms than when pollen levels are low.

The traditional analysis for both studies showed lower mean itching and redness scores for OPATANOL than placebo, but statistically significant differences were only shown at some visits, while at other visits there is little or no difference. In the slope analysis, there was about 50% or more reduction in the slopes for itching and redness in both studies, suggesting OPATANOL reduces tendency for the signs and symptoms to increase as pollen levels increased. The slopes analysis shows a statistically significant ($p<0.05$) difference between OPATANOL and placebo for both C-98-37 and C-00-16.

The clinical relevance of this statistical difference was illustrated by measuring how many patients exhibit significant levels of signs and symptoms. Significant itching and redness was defined as a score greater than 2 (corresponding to a report of “Frequently”, “Very Frequently” or “Continuously”). In both studies, the proportion of patients who had significant (>2 score units) itching or redness was less for OPATANOL than for placebo. The proportion of patients with significant itching or redness increased with increasing pollen levels for patients treated with placebo. The proportion of patients with significant itching or redness was much smaller for OPATANOL and did not increase with increasing pollen levels. Nevertheless, this retrospective responder analysis should be considered with caution.

Concerns were raised regarding the relevance of the slopes analysis used in the placebo-controlled studies but the slopes analysis were considered as supportive of the efficacy of OPATANOL, even if the slope analysis has not yet been validated.

Preventive effect was not considered to have been demonstrated. The approach of demonstrating both a treatment effect and a prevention effect (in the placebo-controlled studies) does not appear appropriate. On one hand, a low score at inclusion for the sign(s) and symptom(s) chosen as primary efficacy parameters must be presented for the demonstration of prevention. On the other hand, a higher score at inclusion must be presented for the demonstration of a treatment effect.

Regarding the differences between subjective and objective measurements, the company outlined that symptoms seen in the patient in the consulting rooms are often less than those given in the history, probably due to removal from the offending environment.

Safety

Olopatadine administered one to four times daily for up to 120 days or more as monotherapy, adjunctive therapy or by eye treatment was safe and well tolerated in both normal subjects and patients. Adverse events were for the most part mild to moderate, and usually resolved without treatment. The most common ocular adverse events were ocular discomfort (burning and stinging).

Benefit/risk assessment

Taking into account that olopatadine showed:

- a high affinity for the histamine H_1 receptor,
- No specific safety issue,
- To be effective in the conjunctival allergen challenge studies,
- To be non inferior to cromolyn sodium and to not substantially deviate from levocabastine (even if olopatadine showed superiority only at day 42) in environmental studies in the treatment of symptoms of seasonal allergic conjunctivitis,
- To be superior to placebo in a supportive (though as yet unvalidated) analysis taking into account pollen levels (slope analysis) in two placebo-controlled studies,

the CPMP considered that the benefit/risk assessment of olopatadine was positive in the treatment of "ocular signs and symptoms of seasonal allergic conjunctivitis".

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of OPATANOL in the treatment of ocular signs and symptoms of seasonal allergic conjunctivitis was favourable and therefore recommended the granting of the marketing authorisation.