London, 19 May 2006
Product name : **OPATANOL**
Procedure no: **EMEA/H/C/000407/X/0004**

SCIENTIFIC DISCUSSION

1 Introduction

The aim of this discussion is to provide the status of the CHMP assessment at the time of the withdrawal of Opatanol 6mg/ml, nasal spray. The assessment was not finalised at this stage, and some of the issues raised were still under discussion. As a consequence the CHMP could not draw definite conclusions on the benefit/risk balance of the product.

1.1 Problem statement

Allergic rhinitis is a clinical condition associated with an excessive generation of specific IgE in response to an allergen and is characterized by the anterior nasal symptoms of sneezing, discharge, itching and stuffiness. Clinically, it is generally recognized that seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) are different, though related, parts of the same overall disease - allergic rhinitis with a common underlying pathology. Although the specific symptoms of allergy in PAR and SAR patients may differ in relative magnitude, the immune mediator pathways leading to expression of those symptoms are virtually identical.

The symptoms of AR may be present for part of the year (seasonal) or throughout the year (perennial) depending on the nature of the allergic sensitivity. For seasonal allergic rhinitis (SAR), the specific IgE is usually directed towards outdoor allergens (e.g. tree, grass, or weed pollens, and fungal spores) with a defined periodicity (e.g. spring or fall). In contrast, perennial disease (PAR) is usually associated with sensitivity to indoor allergens such those related to house dust mites and animal fur.

Oral antihistamines are effective in reducing the nasal and ocular signs and symptoms of seasonal allergic rhinitis and are recommended for use as first-line therapy. Intranasal antihistamines are also recommended as therapy for allergic rhinitis, and are thought to be more effective than oral antihistamines in reducing nasal congestion.

1.2 About the product

Olopatadine is an antihistamine capable of antagonising histamine at the end organ. It was proposed that Olopatadine Nasal 0.6% be indicated in patients 12 years of age and older for the management and treatment of the symptoms of seasonal and perennial allergic rhinitis such as congestion (stuffy nose), rhinorrhoea (runny nose), itchy nose, sneezing, and itchy and watery eyes.

1.3 Main Concerns raised by the CHMP at the time of the withdrawal

At day 120, the CHMP had raised the following main concerns:

- **Clinical aspects**

Efficacy

The efficacy of olopatadine nasal spray relative to other antihistamines or to other treatments is unknown. The lack of active comparator studies in both seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), which is recommended in current CHMP guidelines, is not acceptable and results of such studies should be provided. For SAR the applicant should at least provide the results from the ongoing study C-04-70.

- **Non Clinical aspects**

Toxicology

Two impurities, SOX and RC-3, were negative in the Ames test, positive with and positive or equivocal without activation in the mouse lymphoma assay, equivocal in the SHE assay and negative when tested together with a 9 times higher dose of olopatadine in the mouse micronucleus test. For

both compounds, a 6-month carcinogenecity test is underway in the C57/BL6 p53± mouse, which is generally acknowledged to be sensitive to genotoxic agents. These findings indicate that these impurities could be carcinogenic in man. In either case, the MHE exceeds the acceptable intake level of 1.5 µg/day by one order of magnitude. Since allergic rhinitis is a relatively harmless disease and treatment may be protracted, it is recommended that approval of the proposed line extension be postponed until the ongoing short-term carcinogenecity tests in the C57/BL6 p53± mouse have been completed with unequivocally negative results

1.4 Quality aspects

Drug substance

Olopatadine hydrochloride is a well-characterized drug substance. It has been approved in the EU for use in Opatanol 1 mg/ml eye drops, solution (EU/1/02/217/001-2). A copy of the Drug Substance Sections in the CTD format for olopatadine hydrochloride as presented in the MAA for Opatanol eye drops is provided. As a result documentation on the drug substance has not been re-assessed.

Drug Product

The product is presented as a preserved aqueous solution in a metered dose spray pump. The primary container is a HDPE bottle, with a crimp-on Valois VP-7 metered-dose spray pump and fitted with a polypropylene actuator and HDPE overcap. The formulation uses pharmacopoeial excipients. The preservatives chosen are commonly used and povidone is included as a solubility enhancer to achieve a solution concentration of 0.6%.

Extensive pharmaceutical development studies have been conducted in compliance with the "Draft guideline on the Pharmaceutical Quality of Inhalation and Nasal Products". These include packaging compatibility studies, minimum fill justification, delivered dose uniformity through container life, actuator deposition, droplet size distribution, priming requirements, temperature cycling and robustness.

The manufacturing process is simple and involves dissolution and treatment of povidone, dissolution of olopatadine and other ingredients, pH adjustment followed by filtration and filling. Appropriate in-process controls are described and adequate validation data has been provided to support the manufacturing process.

A comprehensive finished product specification is provided, some clarifications are required and the applicant is asked to tighten the drug substance shelf-life specification. Otherwise, the specification is acceptable. Analytical procedures are described in detail and appropriately validated.

Stability data is provided on 5 primary stability batches, these are all manufactured at the proposed manufacturing site according to the proposed manufacturing process. The characteristics studied include all parameters routinely tested in the drug product shelf-life specification and also include preservative efficacy testing according to the Ph Eur and leachates. The overall stability data show that Olopatadine Nasal 0.6% fully complies with the specification for 78 weeks at 25°C/60% RH/Upright and Horizontal.
Differences have been observed between stability results for samples stored in an upright orientation and for those stored in a horizontal orientation. In order to minimize the levels of degradation products, upright storage will be specified on the drug product label. Nevertheless, samples stored in the horizontal position meet the established shelf-life specifications. An expiry period of 104 weeks is requested with no storage precaution, this is acceptable. A caution to store the container upright will be included on the label.
The proposed in-use shelf-life of this product is 60 days after opening is supported by in-use testing data.

In conclusion both the drug substance and drug product have been sufficiently studied to ensure compliance with the relevant guidelines and batch to batch consistency.

However, the CHMP had raised questions regarding a few minor quality issues. At the time of the withdrawal, these issues remained unresolved.

1.5 Non-clinical aspects

Pharmacology

Olopatadine has anti-allergic and antihistaminic activity, showing stronger activity in animal models than other anti-allergic drugs. *In vitro*, olopatadine is highly selective for H_1, H_2 and H_3 receptors without significant interaction at alpha-adrenergic, muscarinic-cholinergic, dopamine, potassium and calcium channel proteins and numerous other physiologically relevant receptors. In addition there was no effect of olopatadine on cyclooxygenase and 5-lipoxygenase activity. Significant interaction was noted at the Serotonin 2 and Serotonin Uptake receptors, with IC_{50} values in the range of 1 μM and 10 μM, respectively (>100-fold anti-histaminic concentrations). Olopatadine inhibits eicosanoid production by mast cells, suggesting that prostaglandins and leukotrienes will be reduced at the site of the allergic reaction. Olopatadine inhibits the release of cytokines IL-6 and IL-8 from histamine-stimulated human epithelial cells and of histamine and TNF-alpha from human mast cells.

In this application for a nasally applied dosage form, the applicant have provided literature reports that demonstrate the efficacy of olopatadine in animal models of allergic rhinitis, sneezing, nose-scratching, nasal mucous membrane vascular permeability, and effects on eosinophil infiltration and integrin exposure. The effects were dose dependent at oral dose levels > 0.3 mg/kg and when administered topically at concentrations of about 50 microg/ml. The studies in general show the efficacy of the oral dosage form, and only one study included a nasal formulation. The pharmacokinetic studies support an intranasal dose administration, but it is considered that the lack of pharmacodynamic studies using the final formulation of the product may be one potential limitation to the application. It is not considered that this will impact on patient safety, and so the issue is not a major concern. Also, the proof of principle, that olopatadine is effective as an antihistamine agent and is active topically (as per the eye drop application) has been demonstrated.

Olopatadine may be considered relatively safe at the dosages recommended for intranasal administration. General safety pharmacology studies demonstrated no effect on central, peripheral, autonomic, GIT, respiratory or cardiovascular systems at the recommended clinical doses. Doses of three orders of magnitude greater than those recommended clinically were noted to have effects on respiration and behaviour. Olopatadine's lack of CNS system effects was consistent with H_1-receptor occupancy studies suggesting that olopatadine does not effectively cross the blood brain barrier. No effects on heart rate, ECG, or respiratory rate were observed at doses < 5 mg/kg IV in rats and dogs. Olopatadine did not prolong the QTc interval following orally administered doses ≤ 30 mg/kg to conscious dogs and the IC_{50} for the HERG potassium channel was 3-4 orders of magnitude greater than that of terfenadine and of systemically effective anti-allergic/anti-histaminic doses of olopatadine. Thus, adverse effects were observed only following systemic doses of olopatadine greatly in excess of the proposed human dose. The potential for pharmacodynamic interactions is unlikely.

Pharmacokinetics

There are no remarkable findings from the preclinical pharmacokinetic studies. Kyowa pharmaceuticals initially investigated the absorption kinetics of an intranasal gel formulation. Absorption was dose proportional, rapid (Tmax = 5 min) and complete. Alcon have supplemented this information by performing toxicokinetic studies with the final formulation and have shown that intranasally administered olopatadine is systemically absorbed and that the plasma concentrations achieved are comparable to those achieved after oral administration of similar doses. Systemic bioavailability was about 50% in rats, 80 to 100% in dogs, and about 60% in humans. Elimination half-lives of olopatadine following intranasal dosing ranged from about 3 hours in rats to 10 hours in

humans. No accumulation of dosing occurs. Olopatadine is distributed to its site of action, as well as to the GIT (swallowed portion) and excretory organs after intranasal dosing. It was shown that it is the systemic absorption of olopatadine that is responsible for distribution to the respiratory tract (concentration in respiratory tract 210-780 fold lower than those in oesophageal contents). Olopatadine is not significantly metabolised. The main human metabolites are olopatadine N-oxide and N-desmethyl olopatadine. Olopatadine was not shown to interact with microsomal enzymes in the liver, and therefore pharmacokinetic interactions are not predicted after intranasal dosing. The drug is mainly excreted in unchanged form. Following intranasal dosing, plasma concentrations are low (300-fold) than those following a safe oral dose of 400 mg. This information as well as the low systemic accumulation and low potential for drug interactions give olopatadine a wide margin of safety.

Toxicology

The toxicology studies that were used to support the eye drop formulation were used in this application and included the studies performed by Kyowa pharmaceuticals for the oral dosage formulation. The acute oral toxicity of olopatadine was low, with LD_{50} > 1 g/kg in mice, > 3 g/kg in rats and > 5 g/kg in dogs. Repeat-dose oral toxicity studies were conducted in rats and dogs for up to 52 weeks. The NTEL was 6 mg/kg/day in rats and 5 mg/kg/day in dogs, based on minor changes in body and organ weights. Tests for genotoxicity were negative. Oral carcinogenicity studies conducted in rats (104 weeks) and mice (78) weeks did not reveal any treatment-related changes in tumour incidence. Oral administration of 400 mg/kg to rats before pregnancy caused reduced conception and implantation rates attributed to maternal toxicity. When administered orally, olopatadine was non-teratogenic in rats and rabbits, but caused reduced foetal weight in rats treated with 600 mg/kg/day during organogenesis. In three separate peri- and postnatal development studies in the rat, pup body weight gain was consistently reduced at dose levels ≥ 4 mg/kg/day, presumably because of the excretion of olopatadine in the milk. Olopatadine tested negative for antigenic potential in mice and guinea pigs and was non-sensitising in the guinea pig maximization test.

Single dose toxicity studies with the intranasal dosage form showed that the drug was well tolerated as 12 doses of 50 µl per day to rats did not result in any toxicity. Repeated dose toxicity studies were conducted in rats and dogs and ranged from 2 week and 6 month studies (rats) to nine- month studies (dogs). No significant toxicity was noted in these studies using concentrations up to 1.5% olopatadine. In the 6-month rat study, the maximum AUC value was 86.2 ± 5.7 ng.hr/mL (0-2h) in high-dose females, whereas the maximum AUC value in dogs was 1180ng.h/mL (0-4h). In humans, the $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}\infty}$ values were 78 and 91 ng.h/mL, respectively, in SAR patients treated with Opatanol 6mg/ml nasal spray twice daily for 2 weeks. Although these AUC values cover different time spans and are not directly comparable, it is evident that there is a substantial safety margin for systemic effects. This is further corroborated by the previously submitted results of repeat-dose oral toxicity studies in which the lowest NTEL values were 6 mg/kg/day in rats (in a 13-week study) and 5 mg/kg/day in dogs (in a 52-week study) whereas the maximum human exposure to the proposed nasal spray is 0.1 mg/kg/day of olopatadine in a 50-kg patient. Overall, these findings suggest that the proposed extension has a wide safety margin for systemic toxicity.

Local tolerance to the nasal mucosa was assessed in the course of the nasal toxicity studies reviewed above. The only olopatadine-related positive finding was a reversible, trace to mild decrease in the amount of mucin in the goblet cells of the nasal septum in the single-dose rat study. The proposed formulation was also evaluated in a conventional rabbit test for irritant effects by accidental administration to the eye. The test comprised two strengths of olopatadine solution (0.6 and 1.5%) as well as a topical ocular spray out of the final nasal container closure system. Under each condition of application the proposed nasal formulation was practically non-toxic to the rabbit eye.

Although initial characterizations of the toxicity of both the N-oxide and AL-2803 (SOX) degradation products of olopatadine were completed by Kyowa, their development work did not contain studies to biologically qualify the AL-38787A (RC-3) degradation product. Alcon have qualified these two degradation products as per ICH Q3B guidance. 90-day toxicity studies and genotoxicity studies were conducted and the company consider that these products are qualified at the proposed product

specifications of no more than (NMT) 0.6% and 0.3% of active drug substance for the principal degradation products AL-2803 (SOX) and AL-38787A (RC-3), respectively.

In a 13-week intranasal toxicity study in rats including drug substance spiked with up to 0.8% RC-3 and up to 1.2% SOX, there were no findings attributable to either impurity. Both impurities were negative in the Ames test, positive with and positive or equivocal without activation in the mouse lymphoma assay, equivocal in the SHE assay and negative when tested together with a 9 times higher dose of olopatadine in the mouse micronucleus test. Positive results in the mouse lymphoma assay may be considered an expected finding because detection of aromatic aldehyde genotoxicity with exaggerated sensitivity in the mouse lymphoma assay has been reported previously in the literature (Wangenheim and Bolesfoldi, 1988). In the case of AL-38787A the genotoxicity detected was decreased by metabolic activation and the mutation frequencies detected at positive doses were only a little more than 2-fold that of the controls. DEREK analysis did not detect any structural alerts. Therefore according to the work conducted by Wangenheim and Bolesfoldi, 1988, the predictive strength of the positive findings in the mouse lymphoma assay for the carcinogenic potential of AL-38787A is expected to be minimal/limited. The mouse micronucleus test had a NOAEL of 30 mg/kg AL-38787A and represents a 100,000-fold margin for *in vivo* genotoxic potential over the typical human dose in a 50 kg adult. Similar arguments were presented for the AL-2803 degradation product, and the NOAEL in the mouse micronucleus test represents a 40 000 fold safety margin over a typical human dose.

In response to a non-european regulatory agency request, additional repeated dose systemic toxicity tests are being conducted with each of these degradation products. These studies include 28-day repeated-dose range finding studies in C57/BL6 mice and 6-month carcinogenicity studies in p53 transgenic and wild type mice. While final reports are not yet available from any of these studies, the data collected and reviewed to date do not show any effects that would modify the risk associated with exposure to trace amounts of these agents. The reports of these studies will be provided in support of this MAA as they become available.

Since allergic rhinitis is a relatively harmless disease and treatment may be protracted, it is recommended that approval of the proposed line extension be postponed until the ongoing short-term carcinogenicity tests in the C57/BL6 p53± mouse have been completed with unequivocally negative results.

Olopatadine is excreted through breast milk and resulted in developmental problems in offspring, therefore breast-feeding mothers are advised to not use olopatadine.

Povidone is included at 1.8% w/v in the final intranasal formulation. There are a few products on the EU market that have this excipient in their intranasal formulation. The toxicity of PVP to the nasal mucosa was investigated in a 6-month rat study and in a 2-week dog study. It was also assessed in the course of one of two 9-month repeat-dose nasal toxicity studies in dogs. The dog studies were inconclusive. In the rat study, treatment-related findings included a mild dose-related degeneration of the olfactory epithelium and vacuolation of turbinate epithelium consistent with the known effects of PVP monomer. The reversibility of these lesions was not investigated and a NTEL was not established. The expert report states that, after intranasal administration, the molecular weight of povidone administered is larger than that expected to be absorbed into cells and administered material can be cleared from nasal passages by multiple mechanisms. The findings were considered of limited clinical significance.

Fresh Opatanol 6mg/ml nasal spray, Opatanol 6mg/ml nasal spray aged at 40°C to end-of-shelf-life extractable content and Opatanol nasal spray vehicle were tested in a 3-month rat study. All materials contained BAC 0.01% and PVP 1.8%. Treatment-related findings included turbinate adhesions, septal adhesions, turbinate atrophy, remodeling of bone, acute/subacute inflammation, edema and mineralization. The incidence and severity of these lesions were greatest in the aged Olopatadine-treated rats, followed by the vehicle control and then by the fresh Olopatadine-treated rats. The reversibility of these lesions was not investigated and a NTEL was not established.

Taken together, these studies raise concerns about the potential toxicity of Opatanol 6mg/ml nasal spray to the nasal mucosa, particularly in patients undergoing long-term treatment for a relatively benign disorder.

In the ERA, $PEC_{surface\ water}$ for Olopatadine nasal spray and eye drops combined was calculated at 0.00025 μg/L. Since this value is below the trigger point of 0.01 μg/L, no further assessment was made. However, there is an error in the calculation since Fpen should be entered as a percentage rather than a decimal fraction as done by the Applicant. The correct $PEC_{surface\ water}$ is 0.025μg/L which is higher that the trigger value. Therefore, the ERA is incomplete in its present form.

Consequently, the CHMP had raised a number of questions regarding non- clinical issues among which potential toxicity of impurities contained in Opatanol 6mg/ml nasal spray was considered as a main concern. At the time of the withdrawal, these issues remained unresolved.

1.6 Clinical aspects

Pharmacokinetics

The pharmacokinetics following intranasal administration have been adequately characterised.

Olopatadine exhibits linear pharmacokinetics following intranasal doses from 0.1% (0.4 mg) to 0.6% (2.4 mg) and oral doses from 0.5 to 400 mg. Absolute bioavailabilities of intranasal doses of Olopatadine Nasal 0.4% and Olopatadine Nasal 0.6% were 61 and 57%, respectively. Across studies, the mean olopatadine elimination half-life ranged from 8 to 12 hours. Steady-state plasma levels are attained within 3 days of twice-daily intranasal or oral administration.
Twice-daily intranasal administration yielded minimal plasma accumulation (1.1-fold). This extent of accumulation is consistent with that predicted based on linear pharmacokinetics, half-life of 8-12 hours and the twice-daily dosing regimen.

Metabolism and excretion of olopatadine have already been considered in the ocular olopatadine application. Olopatadine undergoes limited biotransformation. The primary metabolic pathways of olopatadine involve N-demethylations and N-oxidation of the dimethylamino-propylidene side chain, hydroxylation of the dihydrodibenz[b,e]oxepine ring at C-8 and sulfate conjugation of the C-8 hydroxyl. At least six minor metabolites were present in plasma including M1 and M2, which represented 3.5% and 1.5% of the total peak radioactivity, respectively. N-desmethyl olopatadine (M1) and olopatadine N-oxide (M3), represent only <6% of olopatadine C_{max}. Unchanged olopatadine was the major constituent in plasma and urine with both identified and unidentified metabolites accounting for <10% of the peak radioactivity in plasma and <10% of the recovered radioactivity in urine.
Urinary excretion was the predominant pathway accounting for 70% of an oral 5 mg ^{14}C solution dose, the overall mean cumulative recovery of radioactivity in the urine and faeces was 87.5% of the dose (C-03-10) with 17% of the dose recovered in the faeces. Approximately 67% was excreted in the first 24 hours of which unchanged olopatadine accounted for 86% of the radiolabelled oral dose recovered in urine. Urinary recovery of metabolites M1 and M3 accounted for 3.8% and 3.1% of the dose, respectively.

The plasma elimination half-life of olopatadine averaged 8-12 hours across studies. Plasma concentrations of olopatadine after twice-daily intranasal doses for 14 days were approximately 1.1-fold higher than those after the first dose indicating minimal accumulation in plasma.
Urinary excretion of olopatadine accounts for the 61% of an intravenous dose and 35-36% of an intranasal dose, while those for M1 and M3 represented about 0.5-0.8% and 1.6-2.0% of the dose, respectively (C-03-11). Estimates of the plasma half-lives of M1 and M3 was dependent on the dose level and route of administration with mean values less or equal to parent drug indicating their elimination was formation-rate dependent.

It is of note that in the study comparing intranasal and intravenous olopatadine, differences in the ratios of metabolites/parent between intravenous and nasal doses may suggest some first-pass metabolism of the intranasal dose.

The pharmacokinetics have been adequately characterised following intranasal administration and there are no specific recommendations for dosing in patients with renal or hepatic impairment, or in the elderly.

However, the CHMP considered a number of questions related to the pharmacokinetics of Opatanol 6mg/ml nasal spray to be addressed to the applicant at day 120 of the evaluation.

Pharmacodynamics

Olopatadine (Z-11[3-(dimethylamino)propylene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride), an analogue to the tricyclic antidepressant doxepin, has been shown to inhibit the activation of mast cells to release mediators, to antagonise histamine in the nasal cavity in antigen-induced rhinitis models in the rat and guinea pigs and prevent activation of eosinophil infiltration in the nasal mucosa of the rat.
In vitro studies have shown its indirect anti-inflammatory activities on preventing eosinophil integrin expression, IL-5 induced expressions of CD11a/CD18 (LFA-1). Olopatadine has been shown to inhibit the production and release of chemical mediators (i.e., leukotrienes and thromboxanes) from various inflammatory cells. Prevention of secretion of pro-inflammatory cytokines may suggest that olopatadine interrupts the chronic allergic cycle. Since olopatadine belongs to a class of agents (i.e., antihistamines) that have been associated with effects on ventricular repolarization (as measured by changes in QT interval), Alcon conducted three cardiovascular safety studies with either multiple twice-daily oral (C-00-23 and C-02-54) or intranasal (C-01-92) doses. Olopatadine does not appear to cause prolongation of the QT interval.

Clinical efficacy

The studies provided suggest that Olopatadine Nasal 0.6% was more effective than vehicle in the treatment of patients (12 years and up) with seasonal allergic rhinitis (SAR). The results in patients with perennial allergic rhinitis (PAR) were less convincing.
Olopatadine Nasal 0.6% was effective in the treatment of the nasal symptoms, sneezing, runny, itchy and stuffy nose (congestion) in SAR patients. These nasal symptoms were effectively treated whether analysed collectively or individually.

Olopatadine Nasal 0.6% treatment of SAR patients resulted in an onset of action of 30 minutes or less, and duration of effect of at least 12 hours, consistent with the proposed BID dosing of two sprays per nostril.
Olopatadine Nasal 0.6% maintained a durability of effect in both SAR patients although results in PAR patients were less convincing.

Olopatadine Nasal 0.6% provided a statistically and clinically significant treatment effect relative to Vehicle in SAR patients dosed BID for two weeks (C-02-37 and C-02-10). Olopatadine Nasal 0.6% treatment resulted in significant therapeutic decreases in baseline reflective TNSS scores (0.9 and 1.0 unit, respectively,) and instantaneous TNSS scores (0.8 and 0.8 unit, respectively) relative to Vehicle. Olopatadine Nasal 0.6% treatment resulted in therapeutic effect sizes of 16.5% to 21.1% in the EEU studies (C-01-83 and C-03-52) and 15.9% to 12.3% in the pivotal environmental (natural exposure) trials (C-02-37 and C-02-10).
It is of note that responses to treatment in C-02-37 were greater in all groups when compared to results for C-02-10. This may possibly relate to the fact that more patients in the latter trial were dosed when pollen levels were low.
The overall TNSS scores were strongly correlated with the reflective RQLQ scores at the end of the study suggesting that the reduction in symptoms was associated with enhancement in the patients' quality of life. In each pivotal environmental study, the reduction in symptoms was accompanied by

an improvement in quality-of-life and ability to work and participate in usual activities with Olopatadine Nasal 0.6% compared to Vehicle treatment.

Olopatadine Nasal 0.6% dosed BID for one year was safe in the treatment of PAR patients (C-01-92). This study had been designed as a safety study and the assessment of efficacy was based on an invalidated questionnaire that could only offer a crude assessment of efficacy. At the end of the PAR study, the average response to the patient rated relief assessment questionnaire was 2.4 for patients who received Olopatadine Nasal 0.6% and 2.6 for patients who received Vehicle. The clinical significance of a change of 0.2 is difficult to assess.
In one of several post hoc "exploratory" anayses Olopatadine Nasal 0.6% demonstrated more than a 50% increase over Vehicle for the percent of visits where patients experienced complete relief vs. moderate, mild, or no relief from symptoms.

Overall, Olopatadine Nasal 0.6% was more effective than vehicle in the treatment of allergic rhinitis in patients 12 years of age and older.

The trials provided can only suggest that the efficacy in seasonal allergic rhinitis of the nasal spray is greater than that of vehicle, and no information is available on how it compares to treatment with other antihistamines or other treatment, it is not possible to define efficacy or indeed benefit risk. It should also be noted that the efficacy in perennial allergic rhinitis (as suggested by the one year study) is not convincing or at best modest.

As a consequence, the CHMP had raised a major concern related to the clinical efficacy of Opatanol 6mg/ml nasal spray.

Clinical safety

The safety profile of olopatadine has already been considered in the application for ophthalmic use. In this application, adverse events in the overall safety population were predominantly non-serious, generally mild to moderate, usually resolved with or without treatment, and generally did not interrupt continuing patient participation in the study.

No deaths or other serious adverse events related to treatment were reported during any studies.

The rate of discontinuation due to adverse events in patients receiving Olopatadine Nasal 0.6% BID/QD in the overall safety population was low (2.8%) and was similar to that observed in patients receiving Placebo BID (3.1%). For patients receiving Olopatadine Nasal 0.6% BID/QD, only 19 (1.6%) patients discontinued study participation due to a treatment-related adverse event. The most common treatment-related adverse events resulting in discontinuation of study participation with Olopatadine Nasal 0.6% BID/QD were headache, taste perversion, nasal discomfort, and epistaxis.

Adverse events were listed as nasal and non-nasal treatment related and non-treatment related. Not surprisingly many adverse reactions occurring in the studies were nasal or related to administration intranasally: epistaxis, nasal ulceration, nasal ulceration, pharyngitis .
The most common treatment-related adverse events included epistaxis and bad or bitter taste.

Consequently, the CHMP considered a number of questions related to the clinical safety of Opatanol 6mg/ml nasal spray to be addressed to the applicant at day 120 of the evaluation.

Evaluation of oral olopatadine and intranasal Olopatadine 0.6% in 3 clinical studies demonstrated no definite evidence of a potential for Olopatadine Nasal 0.6% to prolong the QTc interval relative to placebo.

1.7 Conclusion

In conclusion, the CHMP had addressed a list of questions to the applicant regarding this application, among which the main concerns were related to the efficacy of Opatanol 6mg/ml nasal spray and the potential toxicity of impurities contained in this pharmaceutical form. At the time of the withdrawal, these issues remained unresolved.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AR	Allergic Rhinoconjunctivitis, Allergic Rhinitis
AUC	Area Under The Curve
BAC	Benzalkonium chloride
BID	Twice Daily
CHMP	Committee for Human Medicinal Products for Human Use
CLP	Good Laboratory Practice
C_{max}	Observed Maximum Drug Concentration
CNS	Central Nervous System
CRO	Contract Research Organization
CTD	Common Technical Document
ECG	Electrocardiogram
EEU	Environmental Exposure Unit
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
Fpen	Penetration Factor
GCP	Good Clinical Pratice
GIT	Gastro Intestinal Tract
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HERG	Human Ether-A-Go-Go Related Gene
IC_{50}	Median Inhibitory Concentration
ICH	International Conference On Harmonization
IgE	Immunoglobulin E
IL	Interleukin
IRB/IEC	Independent Ethics Committees
ITT	Intent-To-Treat
LD_{50}	Median Lethal Dose
M1	Metabolite 1: N-desmethyl olopatadine
M2	Metabolite 2: N-didesmethyl olopatadine
M3	Metabolite 3: olopatadine N-oxide
MAA	Marketing Authorisation Application
Max	Maximum
mcg or µg	Microgram
mg	Milligram
MHE	Maximum Human Exposure
Min	Minimum
ml	Milliliter
N	Number Included In Analysis
NfG	Note For Guidance
ng	Nanogram
NMT	No More Than
NOAEL	No Observed Adverse Effect Level
NTEL	No Toxic Effect Level
Olopatadine Nasal 0.2%	Olopatadine Nasal Spray 0.2% (2mg/ml)
Olopatadine Nasal 0.4%	Olopatadine Nasal Spray 0.4% (4mg/ml)
Olopatadine Nasal 0.6%	Olopatadine Nasal Spray 0.6% (6mg/ml)

Abbreviation	Definition
PAR	Perennial Allergic Rhinitis
PEC	Predicted Environmental Concentration
PhEUR	European Pharmacopeia
Placebo	Olopatadine Nasal Vehicle
PVP	Polyvinylpyrrolidone
QD	Once Daily
QTc	Corrected QT Interval
RH	Relative Humidity
RQLQ	Rhinoconjunctivitis Quality Of Life Questionnaire
SAR	Seasonal Allergic Rhinitis
SHE	Syrian Hamster Embryo
T_{max}	Time At Which Maximum Drug Concentration (C_{max}) Occurs
TNSS	Total Nasal Symptom Score including runny nose (rhinorrhoea), stuffy nose (congestion), itchy nose and sneezing
µl	Microlitre
µM	MicroMolar