SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Aerius. This scientific discussion has been updated until 1 July 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Aerius, with the active ingredient desloratadine (DL), is a H_1 antagonist intended for relief of symptoms associated with seasonal allergic rhinitis. The indication was extended to allergic rhinitis and to include Chronic Idiopathic Urticaria through Type II variations.

Desloratadine is the major active metabolite of loratadine and possesses qualitatively similar pharmacodynamic activity with a relative potency approximating 10 to 20 times that of loratadine *in vitro*, and 2.5 to 4 times that of loratadine in animals. Desloratadine is to be given in a daily dose of 5 mg/day.

Seasonal allergic rhinitis (SAR) is an IgE-mediated inflammatory disease of the nasal mucosa characterised by symptoms of sneezing, rhinorrhea, nasal congestion, and nasal pruritus. SAR may be accompanied by itching of the throat, eyes and ears, epiphora and oedema around the eyes. Around 20% of cases are accompanied by asthma. The prevalence of SAR amongst patients attending general practitioners is 11 per thousand in Denmark and 20 per thousand in the UK.

Avoiding allergen exposure is the most effective way of controlling allergic conditions; however, in SAR, total avoidance is almost impossible and as a consequence pharmacological treatment may be needed. Antihistamines are effective in allergic rhinitis, which comprises approximately 80% of rhinitis found in children and 30% in adults. They are effective against rhinorrhea, itching and sneezing but have little effect on nasal obstruction. Clinical trials have shown that, in seasonal allergic rhinitis, between 40 and 80% of patients experience good to excellent symptom relief (approximately twice that induced by placebo).

In the pharmacological treatment of SAR, oral H_1 receptor antagonists are one of several therapeutic options available and have been proven to be effective as initial therapy in many patients with mild SAR, especially controlling rhinorrhea, sneezing and nasal pruritus. Because antihistamines most effectively block receptor sites before histamine release, best results are obtained when they are administered on a regular basis and as a prophylactic measure prior to allergen exposure.

The primary goal of H_1 receptor antagonist treatment in SAR is to reduce and eventually to free the patient from symptoms. Therefore, the most popular test for evaluating H_1 receptor antagonist efficacy in SAR is to use a 3- to 4-point scale from absence to very severe presence of key symptoms attributed to SAR. The primary symptoms being evaluated are nasal congestion, sneezing, rhinorrhea, itchy nose/palate/throat and ocular symptoms. To assess the true effect of the study drug, the use of a placebo group is absolutely necessary because exposure to allergens is variable and the improvements in symptom scores following placebo easily reach 20 to 30%.

Historically, allergic rhinitis is subdivided into two clinical syndromes referred to as SAR and Perennial Allergic Rhinitis (PAR). These classifications are based on the clinical manifestation of AR symptoms in relationship to duration of exposure to differing classifications of allergens. For example, SAR symptoms typically occur in tandem with the pollen season since SAR is triggered by episodic exposure to outdoor allergens (such as pollen and moulds). PAR symptoms typically occur throughout the year since PAR is the result of continual exposure to indoor allergens (dust mites, insects, and animal dander).

In reality, the division between SAR and PAR is not straightforward because PAR and SAR significantly overlap with respect to pathophysiology (i.e., IgE-mediated inflammation), clinical expression of the disease, and therapeutic management (allergen avoidance, antihistamines, decongestants, and intranasal steroids). Firstly, it is often difficult to differentiate between seasonal and perennial symptoms. Patients with either condition complain of nasal itching, sneezing, rhinorrhea, and nasal congestion although, nasal congestion is more pronounced in PAR than in SAR and eye itching tends to be less severe. Secondly, PAR symptoms are usually present on a chronic

basis, however, SAR symptoms may, likewise, be year-round in warm climates where pollens and moulds are perennial allergens (e.g., Parietaria pollen allergy in the Mediterranean area, grass pollen allergy in Southern California or Florida). Even more confusing, symptoms of PAR may not be year-round in climates where exposure to perennial allergens is not similar throughout the year. Thirdly, most patients are sensitive to both indoor and outdoor allergens, and in these patients, seasonal symptoms trigger exacerbations of perennial symptoms.

Other patients may be sensitive to multiple types of seasonal pollens and therefore have symptoms throughout the year. In summary, there is considerable overlap with respect to type and duration of symptoms experienced by PAR and SAR patients.

Urticaria is rarely a serious illness, however, it is a common complaint. Up to 10% of the population (lifetime prevalence) will have an episode of urticaria (all types), although it is difficult to obtain precise figures. The newest conducted studies point to a female: male ratio of about 1.5:1.0. Urticaria may be Acute (duration of episodes of hives less than six weeks) or Chronic (duration of urticaria for six or more weeks).

Chronic Idiopathic Urticaria (CIU) with or without angioedema is defined as the occurrence of frequent urticaria characterised by episodic or persistent wheals, which recur for a minimum of 6 weeks but frequently over months or years. The true incidence of CIU remains unclear. The percentages vary from 0.25-5% in the entire population. CIU patients, in whom history and laboratory tests fail to disclose an underlying cause, account for 80-90% of all cases of chronic urticaria. Though the cause of CIU is unknown, mast cell mediators, of which histamine is the best known, play an important role in the pathogenesis of this disease. The symptoms of CIU may be extremely troublesome for many subjects and may cause significant impairment of their quality of life. The lesions are associated with severe pruritus and may be accompanied by a stinging or somewhat painful prickling sensation.

The histamine H1-receptor antagonists are important first-line medications for the symptomatic treatment of urticaria. However, the use of the classical H1 antihistamines is often accompanied by undesirable side effects, particularly central nervous system (CNS) symptoms such as sedation and anticholinergic effects such as dry mouth. The development of the nonsedating second-generation H_1 antagonists, largely free of the side effects of older antihistamines has been a major advantage for the symptomatic treatment of urticaria.

Pruritus is the hallmark symptom of urticaria and is generally responsive to the administration of an antihistamine. Other efficacy assessments relevant to urticaria include number and size of hives, interference with sleep and daily activities, overall condition and therapeutic response.

2. Part II: Chemical, pharmaceutical and biological aspects

Aerius is authorised as 5 mg film-coated tablets, 5 mg oral lyophilisates and 0.5 mg/ml syrup.

Film-coated tablet

Composition

Aerius is presented as a round, film-coated, embossed tablet with a light blue colour containing 5 mg desloratadine, INN. Other components of the tablet core are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, maize starch, and talc. A two-stage tablet coating employs a first spraying with the blue coating material followed by a clear coating material (dispersion of the coating materials in water). The coated tablets are polished with cannuba wax and white beeswax.

Desloratadine 5 mg tablets will be packed in blister packs consisting of PCTFE/PVC (forming film) and aluminium foil with vinyl heat seal coating (lidding).

Active substance

Desloratadine is manufactured from loratadine, and chemical and spectroscopic data confirm the assigned structure. The active substance can exist in two polymorhpic forms, but this has no clinical consequence as they are bioequivalent and have the same dissolution and stability profile.

The specification contains relevant, validated tests for identity, assay, related impurities etc., sufficient to routinely control the quality in a satisfactory way. The impurity limits in the specifications for the active substance are justified by the toxicology studies.

Batch analysis results of 19 batches are presented, including batches used in preclinical safety, clinical and stability studies. The data are in conformance with the proposed drug substance specifications.

The stability data studies indicate that there is no significant change or trend after storage at 4°C, 25°C or accelerated temperature/humidity conditions. The results support a re-test period of 24 months.

Other ingredients

The ingredients calcium hydrogen phosphate dihydrate, microcrystalline cellulose, maize starch, talc, cannuba wax, white beeswax and purified water all comply with the European Pharmacopoeia. These excipients do not originate from animal sources and are therefore free of contamination with BSE.

There are two non-compendial excipients used, Blue and Clear coating materials. Blue coating material contains lactose monohydrate, hypromellose, macrogol 400, titanium dioxide (E171) and 3-5 % Indigo carmine lake (E132). Clear coating material contains hypromellose and macrogol 400. Indigo carmine lake (E132) complies with the European Directive 78/25/EEC and the other components listed above all meet the European Pharmacopoeia specifications. The lactose monohydrate used is regarded as uncritical with reference to potential BSE risk.

Satisfactory information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Product development and finished product

Aerius is manufactured by a conventional manufacturing process including fluid bed granulation, tablet compression and tablet coating. A satisfactory process validation has been performed, including granulation, blend time, lubrication blend time, compression force and coating.

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation.

The control tests and specifications for the finished product are adequately drawn up. The company has, however, been asked as a follow up measure to re-evaluate and if necessary, tighten the limits for degradation products in the finished product specifications, as soon as the 36 months stability data are available. The identity of desloratadine is based upon retention time (HPLC) and upon R_f (TLC). The HPLC system used for assay and monitoring degradation products in the finished products is the same as used for the active substance.

The dissolution test is carried out with a validated automatic dissolution measuring system (UV-detection). The impurity limits in the product specification are justified by toxicology studies.

Specifications for microbial purity for the finished product are included in the release and shelf-life specifications and conform to the requirements of the European Pharmacopoeia.

The results from 3 production scale batches initially provided for the US site (which is not proposed for the European market) showed loss of excipients during the granulation process. Certificates of analysis for three batches from the proposed manufacturing site in Italy were submitted in the answers to the List of Questions and all results are within specifications.

Stability of the product

A stability study was performed on unprotected tablets when stored for 1 month at 25°C/60%RH, 40°C/75%RH and 40°C/ambient RH. Desloratadine degradation was shown to be mainly accelerated by moisture. The PCTFE/PVC material has high moisture barrier characteristics and although stability data at accelerated conditions (40° C/75%RH) show elevated degradation products levels the results at intermediate stability conditions (30° C/60%) support the selected packaging material. The data justify the inclusion of the warning “Store in original package” on the labelling, in order to protect the product from moisture.

For the finished product stored in the proposed packaging material, intermediate and long-term stability studies have been carried out at different temperatures and conditions (25°C/60% RH (12

months), 30°C/60% RH (6 months)). The major degradation product in desloratadine tablets formyl-desloratadine and total related substances were above the shelf life limit after 6 months storage at 40°C/75%RH. The labelling should therefore include the statement "Do not store above 30°C".

A 24 month shelf life is acceptable, when stored in the original primary package (PCTFE blisters) at a temperature below 30°C.

Discussion on chemical, pharmaceutical and biological aspects

The Aerius tablets are manufactured using a conventional manufacturing process. The chemical-pharmaceutical dossier is well documented and guarantees the quality of the active substance and finished product. The proposed specifications are suitable.

Oral lyophilisate

Composition

Aerius oral lyophilisates contain 5 mg desloratadine, INN. Other components of the oral lyophilisate are gelatine Type B, mannitol, aspartame, polacrilin potassium, dye Opatint Red, flavour Tutti Frutti, citric acid anhydrous and purified water.

The round pink oral lyophilisates (embossed with a "C" on the bottom of the oral lyophilisate) are packaged in unit dose peelable foil/foil blisters consisting of a five-layer cold formable laminate blister material heat sealed with a lacquer coated paper/foil laminate lidding material. This lidding material is to be peeled back by the patient, and instructions are given in section 3 of the package leaflet to that effect. PVC and the heat seal lacquer are the product contact surfaces. The secondary package is either a pouch or a carton.

Active substance

The manufacture and control (including specifications and test methods) of this active substance are identical to that in the dossier for the film-coated tablet. The stability data presented is also identical to that submitted for the film-coated tablets and the claimed retest period has therefore been fully justified.

Other ingredients

Gelatine (Type B), mannitol, aspartame, citric acid anhydrous and purified water comply with the requirements of the current European Pharmacopoeia (PhEur). The gelatine originates from bovine hides, is obtained by alkaline processing and a PhEur certificate of suitability (TSE) (R0-CEP 2000-113-Rev 00) is provided for the stated manufacturer.

Polacrilin potassium complies with the current requirements of the USP/NF with an additional specification for particle size (minimum of 90% < 20 µm). A declaration from the excipient manufacturer is presented which states that no class 1, 2 or 3 solvents are used in the production of this excipient.

The composition of the tutti-frutti flavour is provided, with confirmation that it is in compliance with Council Directive 88/388/EEC. The composition of the proprietary red dye (Dye Opatint Red AD-25000) is provided. All its components are described in the monographs of the current PhEur with the exception of the red iron oxide (E172) which is in the list of authorised colouring materials in the Annex to Council Directive 78/25/EEC. A declaration is provided that this colourant meets the purity criteria of Council Directive 95/45/EC (concerning colours for use in foodstuffs). The in-house specifications for both the tutti-frutti flavour and the Opatint Red AD-25000 are satisfactory.

The packaging consists of a five-layer laminate forming film, polyvinyl chloride (PVC)/oriented polyamide (OPA)/aluminium/OPA/PVC with a PVC product contact surface. The lidding comprises four layers, heat seal lacquer/aluminium foil/polyethylene terephthalate (PET)/bleached kraft paper, with the heatseal lacquer as the product contact surface. Satisfactory specifications are provided for all the primary packaging materials.

Product development and finished product

The objective was to develop a rapidly disintegrating oral solid dosage form containing 5 mg of desloratadine that was easy to take, had an acceptable taste, was physically robust enough to ensure that the dosage could be removed from the package and handled without damage, and could be easily swallowed without water.

The required disintegration characteristics are obtained by the use of the freeze drying technology. A unit dose of an aqueous suspension of the active substance containing the necessary different ingredients is freeze-dried, with the blister package being used as a mould to obtain a tablet shaped oral lyophilisate (dosage unit).

Gelatine and mannitol are the main components, which contribute to the rapid dispersion of the product. Gelatine provides the essential physical structure of the unit and ensures that some flexibility is retained. Mannitol crystallises during the freezing process and gives the unit rigidity. Compatibility of these excipients with the active substance is demonstrated. The gelatine level was fine-tuned to obtain physically robust units that still disperse quickly in the mouth.

Desloratadine is bound on a cation exchange resin (polacrilin potassium) with a resin to drug ratio of 3:1, to reduce its bitter taste.

Citric acid anhydrous is used to adjust the pH of the active substance solution at 6.5, which ensures that desloratadine is appropriately charged for bonding to the resin. A tutti-frutti flavouring agent is then added, with aspartame as sweetener. The selection of these ingredients over other flavouring agents and sweeteners was based on a compatibility study.

The product is coloured pink by the inclusion of Dye Opatint Red AD-25000. For product identification, the letter C is embossed on the bottom of the oral lyophilisate.

Desloratadine can exist in two polymorphic forms, however no crystalline desloratadine was detected in the drug product using X-ray analysis.

The manufacturing process is well described, including the in-process controls and validation studies.

All excipients except polacrilin potassium are dissolved in the pre-lyophilisation solution. The pH is checked as an in-process control and adjusted if necessary (with citric acid). The polacrilin potassium is then dispersed in the aqueous solution. The resultant dispersion is then filled into the blister pockets (with a target weight of 350 mg suspension) and lyophilised. The blisters are sealed with lidding foil.

Process development and validation have been performed in different stages, by the production of the several batches of various sizes (up to full commercial scale). The critical process parameters have been identified and optimised. Results of both in-process controls and finished product tests are given for the batches that are manufactured under optimised conditions and all results comply with the specifications.

The finished product specification includes tests and limits for: description and diameter; identity of colourant; microbial quality (USP methods); uniformity of content; moisture (Karl Fischer); dissolution (0.1 N HCl, first two stages of USP test); identity and assay of desloratadine and content of degradation products of desloratadine (same isocratic HPLC method); tensile strength. The shelf-life limits differ only from the release limits in terms of the content of degradation products.

The identification of the colourant is based on qualitative determination of ferric ions, which are liberated from ferric oxide.

SCH11334 (N-methyl derivate of desloratadine) is the only degradation product observed during long-term stability testing on the finished product and is therefore included as an identified degradation product in the specifications (limit of 0.1% at release). SCH26485 (N-formyl derivate of desloratadine) and SCH 446721 (piperidine hydroxyl analogue), which are only observed in accelerated testing, are controlled by the 0.1% release limit for individual unspecified degradation products. While the release limits for individual degradation products correspond to the acceptance limit in the drug substance (that is, $\leq$ 0.1%), the shelf life limits foresee slight degradation during storage ($\leq$ 0.2%). Limits for total degradation products of $\leq$ 0.2% at release and $\leq$ 0.3% for shelf-life purposes are justified.

The isocratic HPLC method AM535 is demonstrated to separate desloratadine from potential synthesis related impurities (loratadine, DS1 and DS2) and potential degradation products (SCH11334, SCH26485, SCH446721 and SCH13095). There is, however, minimal resolution between two peak pairs (SCH26485/SCH13095 and SCH11334/SCH446721). Gradient HPLC method AM543, on the other hand, is demonstrated to separate all potential impurities from each other and from desloratadine. Specificity of this method is further confirmed by stress studies under different conditions, in which mass balance was demonstrated. Linearity, precision (repeatability, intermediate and reproducibility), accuracy and robustness are demonstrated for the determination of desloratadine and SCH11334 with method AM535 and for the determination of SCH11334 and SCH26485 with method AM543. No correction for response factors of the investigated impurities is necessary. The limits of detection are set at 0.25% and 0.02% for methods AM535 and AM543, respectively. The limit of quantitation is 0.05% for both methods.

All the methods have been adequately validated.

Batch analyses data are given for four pilot scale (stability) batches and one full scale batch manufactured at the proposed site (using active substance batches from both sources), and these demonstrate consistency of manufacture and compliance with the proposed specification.

Stability of the product

Four pilot batches (140,000 tablets) manufactured at the proposed site and packed in the proposed blisters were used in the stability studies. For three of these batches, 18 months results at 25°C/60%RH and 6 months results at 40°C/75%RH are presented. One batch was only used for photostability testing (ICH conditions). Testing was performed according to the proposed specification.

Desloratadine is very stable in the oral lyophilisate, with only low levels ($\leq$ 0.1%) of degradation products being observed during the stability studies at 25°C/60%RH. Degradation product SCH11334 (N-methyl derivate) is not detected immediately after production but slightly increases up to 0.08%. Other levels of degradation products were often below the limit of quantitation ($\leq$ 0.05%). After storage at 40°C/75%RH higher levels of degradation products were reported, although total degradation products for all batches were only 0.2% to 0.3% after 6 months at 40°C/75%.

The diameter of the tablets was observed to be slightly reduced by storage at 40°C/75%.

There were no significant trends in other parameters during either long term or accelerated testing.

In conclusion, the stability data support the shelf-life claimed in the SPC of 24 months with a storage precaution of "Store in the original package." The absence of a temperature-specific storage recommendation is justified.

Syrup

Composition

The syrup is a clear, orange coloured aqueous solution containing desloratadine at a concentration of 0.5 mg/ml. The product is packed in amber glass bottles (Ph. Eur. Type III) closed with a child resistant polypropylene cap. The caps have a polyethylene liner as the product contact surface.
A plastic measuring spoon is supplied with the bottle.

Active substance

The manufacture and control (including specifications and test methods) of this active substance are identical to that in the dossier for the film-coated tablet. The stability data presented is also identical to that submitted for the film-coated tablets and the claimed retest period has therefore been fully justified.

Other ingredients

Propylene glycol, sorbitol liquid (non-crystallising), citric acid anhydrous, sodium citrate, sodium benzoate, disodium edetate, sucrose and purified water comply with the current requirements of the European Pharmacopoeia. The non-compendial excipients are Color E 110 (supplied by Colorcon) and Natural & Artificial Bubble Gum Flavor #15864 (Virginia Dare).

These excipients do not originate from animal sources and are therefore free from BSE/TSE risk.

Product development and finished product

The objective was the development of a stable syrup formulation containing 0.5 mg/ml desloratadine with pleasant organoleptic characteristics, meeting the Ph. Eur. requirements for Preservative Efficacy and amenable to scale-up.

Desloratadine is sufficiently soluble in acidic aqueous solutions to prepare a simple 0.5 mg/ml solution. Stability of the active substance is demonstrated to be optimal in a solution with a pH between 5 and 6. Therefore, a sodium citrate / citric acid buffer is included in the formulation. Stability is further improved by the addition of disodium edetate.

Propylene glycol is used for its humectant, anti-freezing and solubilising properties. Laboratory studies indicated that this excipient can enhance the formation of the formyl-desloratadine degradation product. Accelerated stability studies on products prepared with propylene glycol from different suppliers did not show significant changes in the degradation product content.

Sucrose is used as sweetening agent, although a slight incompatibility with the active substance was shown under stress conditions. Saccharin was not found acceptable from a paediatric point of view. Sorbitol liquid is used as additional sweetener and as anti-cap locking aid. The organoleptic properties are further improved by the addition of the bubble gum flavour and the colorant Sunset yellow (E110). A slight incompatibility between desloratadine and the bubble gum flavour was also observed. The stability of desloratadine in the syrup is however demonstrated in the stability studies presented in part IIF.2.
The selection of benzoate as preservative is based on previous experience. Products containing 100% and 80% of the target concentration (0.1%) are demonstrated to pass the Ph. Eur. Preservative Efficacy criteria for oral preparations.

Although the proposed formulation has initially been accepted by CPMP, the company is requested to further improve the formulation in order to meet current expectations for a paediatric syrup. The company has agreed to assess and, if feasible, implement the following improvements on an ongoing (post-approval) basis:

- The feasibility of removing the colouring agent from the formulation will be investigated to avoid that the medicinal product is unnecessarily attractive to children.

- The feasibility of removing the preservative sodium benzoate from the formulation will be investigated.

Taking into account that the product is intended for long-term use in children, a sugar-free alternative for the currently accepted formulation should be developed.

Stability of the product

The applicant proposes a shelf life of 24 months with the recommendation: "Do not store above 30°C. Store in the original container."

3. Part III: Toxico-pharmacological aspects

Desloratadine has been developed as a H_1 antagonist.

Pharmacodynamics

Film-coated tablet

In-vitro studies

The *in vitro* studies have focused on the radioligand binding to the histamine H_1-receptor (in human recombinant, guinea pig brain and lung and in rat brain) and functional H_1-antagonism on the isolated guinea pig ileum.

These radioligand studies demonstrate that desloratadine has an about 15-fold higher affinity for the H_1 receptor than the parent compound loratadine. The main metabolite, the 3-hydroxy glucuronide, was inactive on H_1 receptor on rat brain membranes.

The specificity of desloratadine for the H_1 receptor was evaluated using a panel of more than 100 receptors and enzymes. These studies revealed that desloratadine had some affinity for H_2, serotonin 5-HT_7 and various subtypes of muscarinic receptors.

Desloratadine antagonised the histamine-induced contractions of isolated guinea pig ileum with an approximately 10-fold higher potency than loratadine. The selectivity ratio of desloratadine, however, was lower than that of loratadine. In this study desloratadine was almost equipotent as anticholinergic and antihistaminic agent with a 4 times lower potency than that of atropine. This finding, however, could be a species peculiarity of the guinea pig. Such species differences have been demonstrated in many instances in the case of G-protein-coupled receptors. Other in vitro and in vivo preclininal studies have clearly shown that the anticholinergic activity of desloratadine is seen only at concentrations and doses which far exceed those, which exhibit antihistamine activity. Furthermore, this activity of desloratadine is not considered to be of clinical relevance as there is no evidence in the clinical dossier, that desloratadine has a significant anticholinergic activity.

In-vivo studies

In vivo studies conducted in mice and guinea pigs, by oral administration, have shown that desloratadine is 2.5-4 times more potent than loratadine. In guinea pigs an oral dose of 0.5 mg/kg (about three times the ED_{50} in this assay) protected 100% of the animals for 8 hours p.a. and 40% at 24 hours p.a. against lethal anaphylaxis induced by i.v. histamine.

Pharmacodynamic drug interactions

In vitro studies using mouse, rat, rabbit, monkey and human hepatocytes and liver microsomes as well as recombinant human CYPs and investigation of the effects of desloratadine on drug metabolising enzymes in subacute toxicity studies were performed.

The preclinical studies do not indicate a clinically relevant potential of desloratadine for liver enzyme induction or drug-drug interactions. However, the applicant has not been able to identify the CYP(s) responsible for the metabolism of desloratadine to 3-hydroxy-desloratadine. The applicant submitted the results of further *in vitro* and *in vivo* studies in their response to the List of Questions. The applicant will perform additional studies to try and identify and characterise the enzyme(s) and report these studies as follow up measures.

General and safety pharmacology

Central nervous system

Desloratadine had no behavioural effect at doses up to 300 mg/kg in mice and 12 mg/kg in rats. In mice it had no anticonvulsant effect up to 160 mg/kg. The lack of activity on the central nervous system is likely due to a lack of penetration through the blood-brain barrier. This is supported by a study in guinea pigs showing that following an i.p. injection of desloratadine (6 mg/kg), the *ex vivo* binding of ^{3}H-mepyramine in the brain was not inhibited, whereas a similar treatment by chlorpheniramine (2 mg/kg) led to a 50% inhibition.

Cardiovascular system

Studies have been performed to evaluate the effect of desloratadine on the QT_c interval and the risk of ventricular arrhythmias. Among the various potassium channels involved in cardiac repolarisation, the HERG channel, mediating the I_{Kr} current is the one that is impaired in most patients with congenital long-QT syndrome and is blocked by some H_1 antagonists.

The following studies were performed with desloratadine: whole-cell patch clamp studies on ventricular myocytes, electrophysiological studies on recombinant potassium channels, electrophysiological and mechanical studies of the guinea pig ventricular muscle, ECG of perfused rabbit heart in Langendorff perfusion chamber and *in vivo* studies in rat, guinea pig and monkey. These studies have revealed some inhibition of the potassium channels with high concentrations of desloratadine. At some targets, loratadine was more potent than desloratadine, but the opposite was

true in other models. The results presented in the dossier are consistent with a recent article showing that among second-generation antihistamines astemizole and terfenadine have a significant inhibitory effect on the HERG channel, whereas loratadine and cetirizine are much less potent (Taglialatela et al, Mol. Pharmacol. 54: 113-121, 1998). The results are also confirmed by the findings of a clinical pharmacology study, in which doses up to nine-fold the therapeutic dose were investigated and no ECG changes were seen.

Gastrointestinal, renal and respiratory function

Single doses of desloratadine (up to 12 mg/kg) do not exert effects on gastric emptying, intestinal transit time, renal and respiratory function.

Summary

Desloratadine is the major active metabolite of loratadine. It is a more potent H_1 receptor antagonist than loratadine itself; however, desloratadine is also a more potent antimuscarinic agent than loratadine when tested at concentrations and doses which far exceed those, which exhibit antihistamine activity. Furthermore, this activity of desloratadine is not considered to be of clinical relevance.

The studies on cardiovascular system revealed no evidence of blockade of cardiac potassium channels (native or injected currents), no prolongation of the action potential (guinea pig papillary muscle), no prolongation of QT_c (animal models and humans) and no evidence of drug induced arrhytmias. The results are furthermore in accordance with the findings of a clinical pharmacology study, in which doses up to nine-fold the therapeutic dose were investigated and no ECG changes were seen. The preclinical results do not indicate any differences between desloratadine and loratadine regarding cardiovascular effects.

Oral lyophilisate and syrup

The mode of action of desloratadine and its activity as a H_1 antagonist have previously been established. No additional information was therefore been submitted or considered necessary by the CPMP.

Pharmacokinetics

Film-coated tablet

The pharmacokinetic profile of desloratadine was studied in mice, rats, cynomolgus monkeys. Desloratadine and its 3-hydroxy metabolite were initially measured by GC/NPD (gas chromatography with a nitrogen phosphorus detector), while LC/MS/MS (liquid chromatography with tandem mass spectrometry) was used in later studies. The glucuronide of 3-hydroxy-desloratadine was measured following hydrolysis by β-glucuronidase.

After single dose administration of desloratadine or loratadine to rats and monkeys a non-linear relationship (less than proportional increases) was noted between C_{max} and dose. In all species, exposure to desloratadine (Cmax and AUC) was higher following administration of desloratadine than after an equimolar dose of loratadine. In rats, gender differences in C_{max} were observed at all doses.

In mice and monkeys the desloratadine AUC was 3 to 4 fold higher after desloratadine than after loratadine, but T_{max} was similar (about 2 hours in mice and 3 hours in monkeys).

Absolute bioavailability of desloratadine was about 50% in male rats as well as in monkeys of both sexes, but about 95% in female rats.

Binding to plasma proteins was approximately 90% in mice and rats and 85% in monkeys and in humans. In rats, distribution was extensive. Tissue/plasma concentration ratio was > 1, especially in liver and bowel. The concentration of desloratadine in foetal plasma and milk were about 40% and 85% of the maternal plasma concentration.

Biotransformation by 5- and 6-hydroxylations predominated in the animals, whilst the 3-hydroxylation followed by conjugation to glucuronic acid was the main process in man. For each species used in preclinical pharmacokinetic studies, the profile of metabolites was qualitatively similar after

desloratadine or loratadine administration. The major (>5%) human metabolites of desloratadine were present in all species after exposure to desloratadine and loratadine. However, animals were not or only to a small extend exposed to 3-OH-desloratadine.

The mean CL/F estimate for humans was 28.5 ml/kg·min, however, individuals with a substantially lower clearance were identified (2.7 and 4.3 ml/kg·min). These subjects had $t_{1/2}$ estimates exceeding 90 h as opposed to 22.8 h in subjects with a normal metabolism.

A small percentage of a desloratadine or loratadine dose was excreted in urine (0.7 to 5%) and faeces (2 to 15%) of laboratory animals as desloratadine. In humans with normal CL/F values, 1.7 and 6.7% of the dose were excreted in urine and faeces, respectively, as desloratadine, and in one slow metaboliser, 25% (urine) and 17% (faeces) of the dose were excreted as desloratadine. The low amounts of desloratadine recovered in urine and faeces indicate that, in laboratory animals and humans (normal metabolisers), desloratadine is metabolically cleared from plasma. In humans defined as poor metabolisers, desloratadine is cleared from plasma by elimination of parent drug in urine and faeces.

Oral lyophilisate and syrup

The pharmacokinetic profile of desloratadine and its 3-hydroxy metabolite has already been established in several species and therefore no additional data have been submitted or considered necessary by the CPMP.

Toxicology

Film-coated tablet

The toxicology program was designed according to the scientific advice provided by the CPMP in May 1998. In view of the studies performed with loratadine, the CPMP considered that chronic studies beyond 3 months would not be necessary if subchronic studies did not reveal toxic effects different from those of loratadine. Furthermore carcinogenicity studies were not considered necessary for desloratadine.

Single dose toxicity

Acute oral and intraperitoneal toxicity was assessed in rats and mice. LD_{50} values after oral administration corresponded to a 3530-6160 fold multiple of the clinical dose. However, single dose toxicity of desloratadine was significantly higher (10 fold) than that of loratadine both in rats and in mice and both by oral or intraperitoneal route; this finding, however, is likely to be due to inherent limitations/artefacts in the acute toxicity studies.

Repeat dose toxicity

Two-week, one-month and three-month toxicity studies comparing desloratadine to loratadine were performed in rats and monkeys.

In rats, the no-effect dose was 3 mg/kg, which was associated with an AUC about 30-fold higher than the AUC in humans receiving the clinical dose of 5 mg. At higher doses, the following effects were observed: vacuolation corresponding to phospholipidosis in eye, brain, heart, lung, liver, intestines, thyroid, muscle and bone marrow, centrilobular hepatocyte hypertrophy, renal tubular dilatation and/or renal tubular cell necrosis, muscle fibrosis and myofiber degeneration, oligospermia and cellular debris in seminiferous tubules, and granulosa cell necrosis. These toxic effects have been observed previously in the loratadine toxicity studies. In general the same effects were observed at 30-60 mg/day desloratadine and 120 mg/day loratadine, except for the testicular effects previously observed at doses as low as 2 mg/kg of loratadine. The reproductive toxicity on testicles of male rats is known from loratadine and other antihistamines and thought to be a species-specific phenomenon.

In monkeys, doses up to 12 mg/kg, associated with an exposure 182-fold higher than the clinical exposure, were generally well tolerated. However, there were minimal phospholipidosis at 12 mg/kg in the three-month study and in the 2-week study a dose of 6.5 mg/kg produced signs of induction of liver microsomal cytochrome P-450 enzymes. As a consequence, the no-effect dose is 6 mg/kg. At higher doses the following toxic effects were noticed: severe emesis, extended abdomen, lethargy,

decrease in serum cholesterol and alkaline phosphatase, cell vacuolation in many organs. In the 3-month study, similar effects were observed at 24 mg/kg desloratadine and 72 mg/kg loratadine.

Genotoxicity

Results from the Ames test, the chromosomal aberration test in peripheral blood lymphocytes and in the mouse micronucleus test (highest dose: 50 mg/kg) were initially submitted, which showed that desoratadine was not genotoxic. Although these assays indicate the absence of genotoxicity, it was stressed that they do not investigate a potential of the major human metabolite of desloratadine (3-OH-desloratadine). The applicant therefore submitted as response to the List of Questions results from a Salmonella/mammalian microsome and Eschericia/mammalian microsome mutagenicity assay and mouse micronucleus assay (highest dose 40 mg/kg) with the desloratadine metabolite 3-hydroxy-desloratadine. The tests did not indicate a mutagenic or clastogenic potential for 3-hydroxy-desloratadine.

Carcinogenicity

According to the scientific advice of the CPMP, no carcinogenicity studies were performed, since exposure to desloratadine was adequate in the loratadine carcinogenicity studies performed previously.

Reproduction toxicity

Studies were conducted in rats and rabbits. Desloratadine (24 mg/kg) administered to male and female rats prior and throughout mating produced body weight loss without altering fertility. In another study where desloratadine was given to male rats for 70 days, a decreased fertility was observed at 12 mg/kg and oligospermia as well as testicular microscopic alterations were observed in a few animals at the 3 mg/kg dose. In rats, no increase in the incidence of malformations was observed up to 48 mg/kg, but foetal weight was decreased at 24 and 48 mg/kg, the no-effect dose being 6 mg/kg. In rabbits, desloratadine did not decrease foetal weight and was not teratogenic at 60 mg/kg and the no-effect dose was 30 mg/kg. In rat perinatal and postnatal development studies, the NOAEL was 3 mg/kg.

Environmental Risk Assessment

An assessment of the environmental risk was performed and no significant risk to the environment related to the use of desloratadine is anticipated.

Discussion on toxico-pharmacological aspects

Desloratadine is the major active metabolite of loratadine. It is a more potent H_1 receptor antagonist than loratadine itself and in most preclinical studies desloratadine AUC was higher after desloratadine than after an equimolar dose of loratadine. The practical consequence is that desloratadine can be used at a 5 mg/day dose, compared to 10 mg/day for loratadine. Beyond that decrease in dose, there is no evidence in the Part III of the dossier that there is another advantage in replacing loratadine by desloratadine. In particular, desloratadine is also a more potent antimuscarinic agent than loratadine when tested at concentrations and doses which far exceed those which exhibit antihistamine activity. Furthermore, this activity of desloratadine is not considered to be of clinical relevance.

The genotoxicity studies showed that neither desloratadine nor the major human metabolite 3-hydroxy-desloratadine are genotoxic.

Oral lyophilisate

No data were submitted for pharmacodynamics, pharmacokinetics, single and repeated dose toxicity, on reproduction toxicology or on mutagenicity as the applicant refers to data submitted in the marketing authorisation application for desloratadine 5 mg.

No carcinogenicity studies were conducted with desloratadine. This was in accordance with the scientific advice of the CPMP, since previously conducted loratadine carcinogenicity studies on rats and mice adequately assessed the carcinogenic risk for desloratadine.

A mucous membrane irritation study was conducted with the DL oral lyophilisate tablet in the hamster cheek pouch (SN 99290). The objective of this study was to assess the mucous membrane irritation potential of the DL oral lyophilisate 5 mg tablet when administered transmucosal to the hamster cheek pouch for five consecutive days. Prior to dosing each hamster was anaesthetised using isoflurane. Six

female hamsters received four tablets on Day 0 (20 mg), two tablets on Day 1 (10 mg) and one tablet (5 mg) on Days 2 through 4. The initial dose of four tablets was reduced due to a possible toxic effect of the DL oral lyophilisate tablet in combination with isoflurane anaesthesia; this was indicated by a longer recovery time from anaesthesia compared with controls. The contralateral cheek pouch of each DL oral lyophilisate tablet-dosed hamster served as an untreated control. Six additional female hamsters underwent physical manipulation (sham dosing) of the cheek pouch. All cheek pouches were examined immediately prior to and ten minutes after dosing.

One DL oral lyophilisate tablet -dosed hamster was found dead on Day 3. The cause of death was not determined during macroscopic examination. However, the death was attributed to the possible toxic effect of the DL oral lyophilisate tablet in combination with isoflurane anaesthesia as mentioned previously. The doses used in this study were 385 (one tablet) to 1541 (four tablets) times the human dose of 0.1 mg/kg based on a 5 mg dose for a 50 kg human.

All DL oral lyophilisate tablet-dosed hamsters showed a very slight to slight redness in the dosed cheek pouch ten minutes after dosing on Days 0 through 4 with the exception of no reaction noted for one hamster ten minutes after dosing on Day 2. In addition, one DL oral lyophilisate tablet-dosed hamster showed very slight redness in the dosed cheek pouch prior to dosing on Day 4. No reaction was noted in any of the sham-dosed hamsters.

In conclusion, DL oral lyophilisate tablets (5mg) were very slightly to slightly irritating to the mucus membrane of the hamster cheek pouch. There were no DL oral lyophilisate tablet-related macroscopic or histopathology findings observed in the hamster cheek pouches associated with the administration of DL oral lyophilisate tablets. The findings in this study do not suggest a significant local irritant effect.

An assessment of the environmental risk was performed and no significant risk to the environment related to the use of desloratadine is anticipated.

Syrup

No data were submitted for pharmacodynamics, pharmacokinetics, single and repeated dose toxicity, on reproduction toxicology or on mutagenicity as the applicant refers to data submitted in the marketing authorisation application for desloratadine 5 mg.

No carcinogenicity studies were conducted with desloratadine. This was in accordance with the scientific advice of the CPMP, since previously conducted loratadine carcinogenicity studies on rats and mice adequately assessed the carcinogenic risk for desloratadine.

An assessment of the environmental risk was performed and no significant risk to the environment related to the use of desloratadine is anticipated.

4. Part IV: Clinical aspects

Film-coated tablet

Desloratadine was initially proposed for the relief of symptoms associated with seasonal allergic rhinitis (SAR). Following a Type II variation the indication was extended to include Chronic Idiopathic Urticaria (CIU). Its mechanism of action is binding as a functional antagonist to the H_1 receptor. Efficacy and safety in SAR has been evaluated in four pivotal, multicentre, randomised, placebo-controlled studies (C98-001, C98-223, C98-224, C98-225) one of which is a phase II dose finding study (C98-001). In addition, four additional studies on onset-of-action were presented. The total number of subjects who received desloratadine in the phase II and III studies (including the additional studies) is 2,346 patients out of the enrolled 3,282 patients. Efficacy and safety in CIU was evaluated in two, pivotal, multicentre, randomised, placebo-controlled, phase III studies (P00220, P00221). The total number of patients receiving 5 mg desloratadine in this indication was 211.

Clinical pharmacology

The pharmacodynamic and pharmacokinetic properties of desloratadine were investigated in both healthy volunteers, patients with hepatic impairment and patients with renal impairment. The 18 studies enrolled a total of 616 subjects employing desloratadine as single oral doses up to 20 mg and multiple doses up to 45 mg/day for 10 consecutive days. The studies were conducted in compliance with GCP.

Overview of trials presenting pharmacokinetic and/or pharmacodynamic data is given in the table below:

Study number	Primary objective/variable	Design	Desloratadine dose/comparator	Study populations
C98-097	Absorption, metabolism, excretion	Single-dose, open label	100 microcuries of ^{14}C-desloratadine in 10 mg, No comparator	6 healthy adult males
C98-215	Effect of food on oral bioavailability	Single-dose, two-way cross over, open label	7.5 mg tablet (w/wo breakfast) No comparator	11 male and 7 female healthy adults
I97-248	Safety and tolerance rising single dose	Single-dose, parallel group	2.5, 5, 10 or 20 mg Comparator: placebo	48 healthy adult males
C98-013	Safety and tolerance rising multiple dose	14 day, parallel-group	5, 7.5, 10 or 20 mg QD Comparator: placebo	49 healthy adult males
C98-214	Dose-proportionality, pharmacokinetic profile, safety	Single-dose, open label, four way crossover	5, 7.5, 10 or 20 mg No comparator	20 healthy adult males
C98-352	Ketoconazole (200mg BID) Interaction	10-day, multiple-dose, two-way crossover	7.5 mg QD (with Ketoconazole or placebo)	12 male and 12 female healthy adults
C98-353	Erythromycin (500 mg TID) interaction	10-day, multiple-dose, two-way crossover	7.5 mg QD (with Erythromycin or placebo)	12 male and 12 female healthy adults
C98-354	Pharmacokinetics in patients with chronic liver disease	Single-dose, open label, parallel group	7.5 mg No comparator Reference: Normal hepatic function	16 male and 4 female adults, 12 with chronic liver disease
C98-355	Pharmacokinetics in patients with chronic renal insufficiency	Single-dose, open label, parallel group	7.5 mg No comparator Reference: Normal hepatic function	26 male and 11female adults, 25 with renal insufficiency
C98-356	Pharmacokinetics in patients with different sex and race	14 day, multiple dose, open label	7.5 mg QD No comparator	48 healthy adults, 24 females and 24 males, 24 black and 24 Caucasian
C98-357	Pharmacokinetics/ electrocardiographic pharmacodynamics	10 days, two ways crossover	45 mg (6 x 7.5 mg) once daily Comparator: placebo	12 male and 12 female healthy adults
P00117	Pharmacokinetics of desloratadine and 3-OH-desloratadine	10 day, open label, three way crossover	5 or 7.5 mg QD Comparator: 10 mg loratadine QD	18 males and 7 female healthy adults
P00272	Pharmacokinetics of desloratadine and 3-OH-desloratadine in hepatic impairment	Multiple dose, open, parallel groups	5 mg once daily for 10 days	10 male, 10 female, 11 with moderate hepatic impairment
P00275	Pharmacokinetics of desloratadine and 3-OH-desloratadine	10 day, open label	5 mg QD No comparator	57 male and 56 female, healthy adults
P00311	Bioavailability of desloratadine polymorphs	Single dose, open label, three way crossover	5 mg of form 1, form 2 and clinical trial formulation No comparator	63 healthy male adults
C98-551	Psychomotor performance with and without alcohol	Single dose, four way crossover	7.5 mg with and without alcohol Comparator: placebo with and without alcohol	14 female and 11 male healthy adults
P01196	Flare response study, pharmacokinetics of desloratadine and 3-OH desloratadine	28 day, blinded, parallel groups	5 mg Comparator: placebo	3 female, 25 male healthy adults
P01380	Influence of grapefruit juice on the oral bioavailability of desloratadine and fexofenadine	Open, single-dose 4-way crossover study	5 mg Comparator: 60 mg fexofenadine	24 male and female healthy volunteers

P01378	Evaluation of the pharmacokinetics and electrocardiographic pharmacodynamics of desloratadine with concomicant administration of Prozac	Open-label, randomised, third-party blind, multiple dose, parallel group study	5 mg with and without 20 mg fluoxetine	54 male and female healthy volunteers
P01868	Evaluation of the pharmacokinetics and electrocardiographic pharmacodynamics of desloratadine with concomicant administration of cimetidine	Randomised, open-label, multiple-dose, parallel group study	5 mg with and without 600 mg cimetidine	36 male and female healthy volunteers
P00090	Effects of a single dose of desloratadine on the flying ability	Blinded, single-dose, 3-way crossover study	5 mg Comparator: placebo and 50 mg diphenhydramine	21 male healthy volunteers

Pharmacodynamics

Cardiovascular pharmacodynamics

This study (C98-357) was a randomised, 2-way crossover, double-blind, multiple dose (10 days), placebo controlled study in which 24 healthy subjects (12F/12M; 18-50 years) were randomised.

The primary objective of this study was to evaluate the electrocardiographic effects (difference between baseline maximum ventricular rate, PR, QRS, QT and QTc intervals and the corresponding day 10 maximum ECG parameters) of desloratadine 45 mg (9 times a daily dose). The secondary objectives of the study were to determine the pharmacokinetic profile of desloratadine and observe the safety and tolerability of the drug. Vital signs and ECGs were performed, and blood samples were collected at pre-specified times for safety and pharmacokinetic evaluations. It is important to stress that subjects with screening ECG QTc values exceeding 420 msec were excluded.

There was a statistically significant increase compared to placebo in the mean ventricular rate by 9.4 bpm and a statistically significant reduction of the QT intervals. No statistically significant changes were detected for the change between treatment groups in QT_c interval between the desloratadine and placebo treatments. Subgroup analysis (by gender) showed that change in ventricular rate was significant in females but not in males and that a significant difference for change of the PR interval was seen for females but not for males. The reduction in QT interval was statistically significant for both males and females.

In conclusion this study in which subjects with a baseline QTc < 420 msec received 9-fold the clinical dose, showed that there was no evidence of clinically relevant prolongation of the QTc interval.

Psychomotor pharmacodynamics

The primary objective of the psychomotoric study (study C98-551) was to evaluate and compare the relative effects on psychomotor performance of desloratadine 7.5 mg with and without alcohol in healthy volunteers. The study was conducted as a single-centre, single dose, double-blind, randomised, placebo-controlled, 4-way crossover study. All subjects (14F/11M, 21-54 years) received all 4 treatments and there was at least a 5-day washout between each treatment. The subjects completed a Digit Symbol Substitution Test (DSST), Serial Add Subtract (ANAM Battery), Psychomotor Vigilance Test, Stanford Sleepiness Scale, and Modified Romberg's Test.

No significant differences in the psychomotor tests were found between the desloratadine 7.5 mg and placebo groups, whether given alone or with alcohol.

The influence of desloratadine on the ability to drive and use machines was investigated in a single dose, 3 way crossover study in 18 healthy volunteers. The results were submitted as part of the answers to the List of Questions. The over-the-road driving test showed the effect of desloratadine to be similar to that of placebo, whereas the active control (diphenhydramine) had significantly worse lateral deviation and longer braking time. The results are reflected in the SPC section 4.7.

The influence of desloratadine on ability to fly was investigated in a single dose, 3-way crossover study in 21 healthy volunteers. Desloratadine 5 mg produced no detrimental effects on tasks related to flying ability, including those tasks addressing vigilance, tracking, and complex task performance or on resource management performance or on subjective sleepiness for the measured period of 1 to 6 hours after drug administration. Diphenhydramine, used as an active control, significantly increased subject sleepiness and impaired performance on flying ability tasks. While the sedative effects of multiple dose treatment were not evaluated in this study, the data from this study are predictive of long-term use of desloratadine as:

1) desloratadine exhibits linear pharmacokinetics, as a result no unexpected accumulation has been observed after 28 days
2) the clinical experience with treatment periods up to six weeks has shown a somnolence rate no different from placebo and
3) there were no reports of sedation following administration of desloratadine 45 mg (nine-fold the clinical dose).

The results were introduced in section 5.1 of the tablet SPC following a Type II variation. Identical wording was later introduced in the SPC of the syrup and oral lyophilisate following a Type II variation.

Pharmacokinetics

The plasma drug concentration assay methods changed during the clinical development. A sensitive and specific LC/MS/MS method for quantification of desloratadine and 3-OH desloratadine was validated with a limit of quantitation (LOQ) of 0.025 ng/ml for both analytes. This method was used in studies C98-352 to C98-357, P00117, P00275, P00311, P01196, and P01380. Studies 197-248, C98-013 and C98-215 used a GC/NPD method, which only quantified desloratadine (LOQ 0.1 ng/ml).

Following oral administration of 5 or 7.5 mg desloratadine, peak plasma concentrations are usually obtained between approximately 2 to 6 hours after dosing. Food has no effect on the extent of desloratadine absorption.

Desloratadine is extensively metabolised and only small percentages of the orally administered dose are recovered in the urine (<2%) and faeces (<7%). The major metabolic pathway of desloratadine is hydroxylation in position 3 to form 3-OH-desloratadine that is glucuronidated and the glucuronide conjugate is subsequently excreted in the urine and the bile. The elimination plasma half-life is about 20 to 30 hours.

Desloratadine has been shown to exhibit linear kinetics over the dose range 5 to 20 mg. Steady state was generally reached by day 7.

In a randomised multiple-dose study comparing the steady state pharmacokinetic profiles following oral administration of 5 mg (once daily) desloratadine with those obtained following multiple dose administration of 10 mg loratadine (once daily), plasma concentrations of desloratadine, 3-OH-desloratadine and 3-OH-desloratadine glucuronide were observed to be very similar.

A phenotypic polymorphism in the metabolism of desloratadine was observed in 8.6% of the population evaluated in the clinical pharmacology studies. The frequency of slow metabolisers is estimated to be about 4% based on the pharmacokinetic study P00275, in which the demographics of the subjects are comparable to those of the general SAR population. In slow metabolisers the half-lives are much longer (greater than 60 hours) andwith median AUC values approximately 6-fold higher. Maximum desloratadine concentration was about 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours. The major route of elimination by a slow metaboliser is via excretion of unchanged drug into urine and faeces. The amount of 3-OH-desloratadine and unchanged drug is less than 10% and over 42% respectively compared to 51% and 8.4% in normal metabolisers. The metabolism does not appear to be mediated by a known cytochrome 450 enzyme. The applicant will perform further studies on the metabolism.

The effects of race (Blacks versus Caucasians) and gender on the pharmacokinetics of desloratadine following administration of 7.5 mg once daily for 14 days were relatively small. On average AUC and Cmax values for desloratadine and 3-OH desloratadine were higher in females (3-10% and 45-48%, respectively) compared with males.

Mean AUC and Cmax for desloratadine were higher in Black compared with Caucasian subjects (18-32%), while mean AUC and Cmax values for 3-OH-desloratadine were lower (10%). Therefore, no dose adjustment is needed for race or gender.

Protein binding to human plasma protein ranges from 83 to 87%.

Studies in special populations (C98-354, P00272, C98-335)

In study C98-354 the pharmacokinetics of desloratadine was investigated in subjects with normal liver function (n=8) as compared to patients with various degrees of stable chronic liver disease (n=12).

The study showed that patients with hepatic dysfunction had mean AUC and Cmax values that were up to 2.3 and 2.4 times greater, respectively, than healthy subjects and that a single-dose of desloratadine 7.5 mg administered to subjects with various degrees of hepatic dysfunction was safe and well tolerated.

In response to the List of Questions interim results were submitted from a multiple dose study (P00272) in subjects with hepatic impairment. The study is a Phase I, open label, multiple dose, parallel group study comparing the pharmacokinetics of desloratadine and 3-OH-desloratadine. The interim results include 20 subjects (10 men, 10 women, 40-66 years, 9 healthy and 11 with moderate hepatic impairment. Normal metabolisers with moderate hepatic impairment could experience a 3-fold increase in the desloratadine exposure (median AUC). However, no apparent difference between the exposure to desloratadine in slow metabolisers with and without hepatic impairment was seen. Given that the increase in median exposure between normal and poor metabolisers is 6-fold and that there is no major differences in the safety profile for poor and normal metabolisers a dose reduction is therefore not recommended in patients with hepatic impairment.

The safety profile of desloratadine in patients with renal insufficiency was studied in a Phase I, single dose study (C98-335), for which the report was submitted as part of the answers to the List of Questions. The study included 37 subjects (12 healthy subjects, 25 patients with chronic renal insufficiency, 26 men and 11 women, 26-70 years). Patients with varying degrees of renal impairment, who were normal metabolisers has a 1.5-2.5 fold increase in AUC for desloratadine and minimal changes in 3-OH-desloratadine concentrations. Therefore a warning concerning the use in patients with renal impairment is recommended. This is reflected in the SPC (see section 4.4 Special warnings and special precautions for use).

The pharmacokinetics of desloratadine were evaluated in 17 subjects $\geq$ 65 years of age who participated in a multiple dose (5 mg, o.d. x 10 days) study. The mean AUC and Cmax were 20% greater than in subjects < 65 years old. The mean plasma elimination $t_{½}$ was prolonged by approximately 30% (33.7 hours). Based on these results dose adjustment in the elderly is not warranted.

Interaction studies (C98-352, C98-353, P01380, P01378, P01868)

No clinically relevant changes in desloratadine plasma concentrations were observed in the ketoconazole and erythromycin interaction studies.

The enzyme(s) as well as the tissue site(s) responsible for the metabolism of desloratadine to its primary metabolite 3-OH-desloratadine has not yet been identified. However, it is anticipated that the potential for PK interactions of desloratadine with classical CYP450 inducers and inhibitors is low, as the metabolism does not appear to be mediated by a known cytochrome P450 enzyme. The inhibition spectra of desloratadine was evaluated using five cytochrome P450 enzymes: CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP2D6 in human liver microsomes. Desloratadine and 3-OH desloratadine did not significantly inhibit any of the five enzymes. This property and that desloratadine is not a substrate or an inhibitor of P-glycoprotein was included in the SPC in Section 5.2 through a Type II variation.

The drug interaction potential of slow metabolisers is considered to be low, because neither desloratadine nor 3-OH-desloratadine inhibits known CYP450 enzymes and because any drug or xenobiotic that inhibits the metabolism of desloratadine to 3-OH-desloratadine would be unimportant since the enzyme is impaired in "slow" metabolisers. Also the safety profile of the subjects identified

as "slow" metabolisers in the ketoconazole (n=8) and erythromycin (n=1) interaction studies were not different from the normal metabolisers in the studies.

Study P01380 evaluated the effect of grapefruit juice on desloratadine and fexofenadine (FX) pharmacokinetics. 19 of the 24 subjects were Hispanic (from the Miami area). The bioavailability of DL, measured in terms of plasma DL and 3-OH DL levels, was unaltered, while FX C_{max} and AUC were reduced by ~ 30 % in the presence of grapefruit juice.

The effects of grapefruit juice are not limited only to inhibition of CYP3A4, but also involve transport mediated uptake and efflux absorption processes, namely OATP and P-gp.

Given the potential importance of these transport processes as discussed in the 'Note for Guidance on Drug Interactions', the information that desloratadine has a low potential for interactions at the absorption site was added to section 4.5 of the SPC through a Type II variation.

The results of two separate controlled, parallel-group clinical pharmacology studies (P01378, P01868), characterising the effects of Fluoxetine and Cimetidine on the pharmacokinetics of desloratadine were submitted in a Type II application. The results showed that CYP2D6 does not play a major role in the metabolism of desloratadine. This is consistent with results from the in vitro inhibition studies that predicted that desloratadine would not produce any clinically relevant inhibition of CYP2D6. The use of fluoxetine was questioned, as fluoxetine itself is a strong CYP2D6 inhibitor. In the response the MAH pointed to two *in vitro* studies submitted in the original Marketing Authorisation application for desloratadine film-coated tablets. These two studies were carried out using two validated probe substances (bufuralol and dextrometorphan) and indicated that high concentrations of desloratadine did not inhibit CYP2D6. That desloratadine administration does not affect fluoxetine metabolism *in vivo* supports the conclusion that clinically relevant inhibition of CYP2D6 is not expected in the recommended daily dose of 5 mg desloratadine. The information on interactions in section 5.2 in the tablet SPC was slightly altered following the Type II variation to state that desloratadine does not inhibit CYP3A4 *in vivo*, and *in vitro* studies have shown that the drug does not inhibit CYP2D6. Identical wording was later introduced in the SPC of the syrup and oral lyophilisate following a Type II variation.

Bioequivalence study

The study was performed as a 3-way crossover bioequivalence study comparing two capsule formulations containing mainly either one of the two polymorph forms of desloratadine with the to-be-marketed 5 mg tablet as reference. The study demonstrated bioequivalence between the two capsule formulations and the reference formulations as well as between the two capsule formulations.

Clinical efficacy in seasonal allergic rhinitis (SAR)

Dose-response studies and main clinical studies

The clinical efficacy and safety studies were conducted according to GCP. The design, dose, duration, the number of patients and the demographic characteristics of these patients are given below:

Study number	**Study design**	**Dose** **Duration**	**N° of patients (randomised/treated/ITT)** **Age range (years)** **Sex distribution**
C98-001	Double-blind, placebo controlled, parallel group, randomised efficacy and safety dose-finding study	2.5mg, 5mg, 7.5mg, 10mg or 20mg o.d. for 14 days	1036/1036/1026 12-75 423M – 613F
C98-223	Double-blind, placebo controlled, parallel group, randomised efficacy and safety study	5mg or 7.5mg o.d. for 14 days	496/496/493 12-72 181M – 315F

C98-224	Double-blind, placebo controlled, parallel group, randomised efficacy and safety study	5mg or 7.5mg o.d. for 14 days	492/492/489 12-73 168M – 324F
C98-225	Double-blind, placebo controlled, parallel group, randomised efficacy and safety study	5mg or 7.5mg o.d. for 4 weeks	475/475/474 12-75 162M – 313F

The symptoms evaluated in the Phase II and III studies were nasal symptoms: rhinorrhea, nasal stuffiness/congestion, nasal itching, sneezing; and non-nasal symptoms: itching/burning eyes, tearing/watering eyes, redness of eyes and itching of ears and palate. In addition, cough was assessed in studies C98-223, C98-224 and C98-225. In all studies the symptoms were assessed using a 4 point verbal rating scale from 0 to 3, with 0 being no symptoms and 3 being severe symptoms.

The symptom scores were collected twice daily, in both a reflective (how the patient has been feeling the preceding 12 hours), and instantaneous or now (how the subject was feeling at the time of assessment) fashion. The former method of data collection provided information on how effective the treatment had been throughout the day, whereas the latter provided information on the efficacy at the end of the entire dosing interval (24 hours). The scores from the eight/nine symptoms were summed up to a total score.

Primary efficacy endpoint was the 2-week average change from baseline of the subjects' total reflective symptom scores. In the onset of action studies the primary efficacy endpoint was the change from baseline in total symptom score and the time to onset defined as the first time point that desloratadine was statistically superior to placebo and remained so thereafter.

Secondary endpoints were: total nasal, total non-nasal and individual symptom scores, overall condition of SAR and therapeutic responses.

The *overall condition of SAR* was evaluated jointly by the investigator/designee and the subject at baseline and all subsequent visits according to the scale below. The score was based on the entire time interval since the last visit, and graded as for severity of signs and symptoms on a four point verbal rating scale from 0 to 3, where 0 is no symptom evident and 3 being severe symptoms.

The subject and physician/designee evaluated the therapeutic response jointly at each visit after baseline on a 5 point verbal rating scale from 1 to 5, with 1 being complete relief and 5 being treatment failure.

In addition, quality of life (QOL) was measured in studies C98-223, C98-224 and C98-225. The QOL variables included the 8 SF-36 scales, the 2-component summary scores of the SF-36, and the 8 scales of the rhinoconjunctivitis QOL questionnaire. Additionally, an overall rhinoconjunctivitis score was calculated as an average of all items. Both the SF-36 and rhinoconjunctivitis-specific HQOL used the past week as the reference period for assessment.

Major exclusion criteria in the trials included asthma (requiring chronic use of inhaled or systemic steroids), current history of frequent, clinically significant sinusitis or chronic purulent postnasal drip, rhinitis medicamentosa, upper respiratory tract or sinus infection that required antibiotic therapy within 14 days prior to screening, or viral upper respiratory infection within 7 days prior to screening, nasal structural abnormalities (large nasal polyps, marked septal deviation) that significantly interfere with nasal air flow and dependency upon nasal, oral or ocular decongestants, nasal topical antihistamines, or nasal steroids.

The Intent-to-treat (ITT) population was defined as all randomised subjects who received at least one dose of study medication and had both baseline and some post-baseline data. All analysis were performed on this population. The Efficacy-Evaluable population was defined as randomised subjects who had no key protocol violations. Confirmatory efficacy analyses on the primary variable were based on this subset of subjects. Assessment of the subjects' evaluability was done prior to unblinding the treatment code.

In the four multiple dose SAR studies the primary efficacy analysis was analysed as per the study protocols using a two-way analysis of variance (ANOVA). Statistical analyses were also performed based on pooled data from the four multiple dose SAR studies. The pooled analyses employed two mixed effects models performed on the pooled 2 week average reflective total symptom score.

Dose-response study (C98-001):

From the preclinical data it is anticipated that the human dose of desloratadine may be equal to ¼ to ½ that of loratadine, and its effect may persist for 24 hours. Therefore, the applicant has chosen to perform its clinical program starting with a placebo controlled dose-finding study with a dose of desloratadine ranging from 2.5 up to 20 mg.

Based on the results of symptom scores and assessment of overall condition of SAR and response to therapy, all of the desloratadine doses except for the 2.5 mg dose were all more effective than placebo in the relief of SAR signs and symptoms.

Primary endpoint (Total reflective symptom score excluding cough)

	Baseline	**Change from Baseline**		**Desloratadine vs. Placebo**	**5mg vs 7.5 mg**
Treatment	Mean	Mean	% change	p-value	p-value
5 mg desloratadine	14.2	- 4.3	-28.0	< 0.01	0.98
7.5 mg desloratadine	13.9	-4.3	-26.7	< 0.01	
Placebo	13.7	-2.5	-12.5		

At almost none of the time points did desloratadine 5 mg o.d. statistically improve the overall condition of SAR as compared to placebo (at endpoint day 15 p=0.13, mean change from baseline - 24.9% versus –19.6%).

Joint subject-physician evaluation of the therapeutic response results showed that desloratadine 5 mg o.d. was not statistically significantly superior to placebo, especially at the later visits. At the two weeks evaluation the mean therapeutic response for 5 mg was 3.33 as compared to 3.56 for placebo (p=0.05) with 3 being moderate relief and 4 being slight relief.

Based on the results of this study the two lowest effective doses of desloratadine 5 and 7.5 mg were chosen for further studies.

Study C98-223

This study demonstrates that both doses of desloratadine (i.e., 5.0 and 7.5 mg o.d.) were statistically significantly more effective than placebo for a majority of the time points in improving total (nasal and non-nasal combined) symptom scores. These statistically significant results were observed in the reflective total symptom score over Days 1-15 (primary endpoint) with a mean change for 5 mg of –27.8% and –21.7% for placebo (p=0.03). The 7.5 mg o.d. dose (but not the 5 mg o.d. dose) was also statistically significantly different from placebo for the AM total instantaneous/now score with a mean change in total score of –27.4% for 7.5 mg compared to –19.5% for placebo (p<0.01).

Comparing desloratadine 5 mg o.d. with placebo at the primary endpoint, statistically significant reductions from baseline in the mean individual symptom scores were restricted to sneezing, tearing/watering eyes and redness of eyes.

At almost none of the time points did desloratadine 5 mg o.d. statistically improve the overall condition of SAR as compared to placebo (endpoint p=0.59, -23.1% versus -22.3%).

As in study C98-001, joint subject-physician evaluation of the therapeutic response results showed that desloratadine 5 mg o.d. was not statistically significantly superior to placebo. Again this was observed at the later visits (endpoint p=0.19, 3.50 for desloratadine 5 mg versus 3.66 for placebo).

Significant HQOL improvement were observed with both doses of desloratadine for some of the HQOL parameters and the overall score (p<0.05 for 5 mg compared to placebo, p<0.01 for 7.5 mg for overall score).

Study C98-224

In this study 5 mg o.d. of desloratadine was numerically better than placebo during early treatment (day 2 - 4) and statistically significantly more effective than placebo at weeks 1, 2 and on average over Days 1-15 in improving total reflective symptom score whether including or excluding cough (p=0.02,

-30.4% versus -21.8% including cough; p=0.02, -30.2% versus -21.7% excluding cough). The 7.5 mg dose was not statistically superior to placebo in reducing total symptom score (including or excluding cough).

In contrast to 7.5 mg o.d., desloratadine 5 mg o.d. was observed to be statistically significantly superior to placebo in reducing AM total instantaneous/now symptom score at the primary endpoint including/excluding cough (d2-15) (p=0.03, -26.7 versus -19.4% including cough, p=0.03, -26.4 versus –19.1% excluding cough). A same pattern of results was observed for the change from baseline in subject-evaluated total nasal and total non-nasal symptom score.

Comparing desloratadine 5 mg o.d. with placebo at the primary endpoint, statistically significant reductions from baseline in the mean individual symptom scores were restricted to nasal itching, sneezing, itchy/burning eyes and redness of eyes.

Desloratadine 5 mg o.d. statistically improved the overall condition of SAR as compared to placebo (endpoint p=0.05, -26.9% versus -18.7%).

Joint subject-physician evaluation of the therapeutic response results showed that desloratadine 5 mg and 7.5 mg o.d. were both statistically significantly superior to placebo (p<0.01, mean at endpoint 3.5 for 5 and 7.5 mg and 3.9 for placebo).

Based on the Rhinoconjunctivitis QoL Questionnaire, the total score as well as some domains, showed statistically significant improvement for desloratadine 5 mg in comparison to placebo.

Study C98-225

Analysis based on the protocol-specified trend test for non-decreasing response with increasing dose resulted in a statistically significant result (p=0.04). In general desloratadine 5 mg o.d. was only slightly numerically more effective than placebo in reducing the total reflective symptoms score whether including or excluding cough (p=0.35, 24.8% versus 22.4%; p=0.41, 24.6% versus 22.3% respectively). Desloratadine 5 mg was also for the total AM instantaneous/now symptom score with and without cough not significantly more effective than placebo (p=0.97, -20.7% for both 5 mg and placebo excluding coughing, p=0.84, -20.9% for 5 mg and -20.7% for placebo including coughing).

The same conclusion can be drawn for the other secondary efficacy parameters (total nasal symptom score as well as the total non-nasal symptom score including and excluding cough). The 7.5 mg o.d. dose scored somewhat better, however, superiority was rather small.

Comparing desloratadine 5 mg o.d. with placebo, no statistically significant reductions from baseline in the mean individual symptom scores were observed.

At none of the time points did desloratadine 5 mg o.d. statistically improve the overall condition of SAR as compared to placebo (endpoint p=0.28, -25.1% versus -20.9%).

Joint subject-physician evaluation of the therapeutic response results showed no statistically significant superiority for desloratadine 5 mg o.d. as compared to placebo (p=0.46, mean 3.7 for both placebo and 5 mg).

Only trends toward improvement in HQOL assessments could be observed.

Pooled efficacy data

To better characterise the effects of desloratadine and to better characterise treatment effects in subgroups of patients a statistical analysis was performed based on pooled data from the 4 major clinical trials. Pooling of data from these studies is appropriate as they had approximately the same number of patients and similar study design. One difference was that cough was not assessed in study C98-001. Statistical analyses of studies C98-223, C98-224 and C98-225 did not show a difference in results whether including or excluding cough from the total symptom score. Consequently efficacy analyses of the pooled data were based on the change from baseline in total reflective symptom score excluding cough. The statistical analyses employed two mixed-effects models. Model #1 extracted effects for study, treatment and study-by-treatment interactions, with study and study-by-treatment being random and treatment being fixed. Model #2 was used to study the effects of co-variates. Model #2 extracted effects for study, treatment, sex, race, sex-by-treatment, race-by-treatment and study-by-treatment interaction. Study and study-by-treatment being random and the other effects fixed.

The pooled analyses (Model #1) for the primary efficacy variable is given below.

Primary efficacy parameter (Total reflective symptom score)

Treatment		**Baseline (mean)**	**Change from baseline**		**Desloratadine versus Placebo (*p - value*)**	**5 mg vs 7.5 mg (*p – value*)**
			Mean	%		
5.0 mg desloratadine	657	16.1	-4.5	-27.7	0.02	0.78
7.5 mg desloratadine	659	16.0	-4.6	-27.4	0.02	-
Placebo	655	16.1	-3.4	-19.4	-	-

For total symptoms from patient diaries during the first 2 weeks of treatment, pooled data showed a mean symptom reduction with desloratadine 5 mg of 27.7% versus a placebo reduction of 19.4% (p=0.02). The mixed-effects model #1 confirmed that the symptom reduction seen following 5 mg was not different from the one seen following 7.5 mg.

Pooled data for secondary efficacy analysis showed similar reductions as those observed with the total symptoms data. Total instantaneous/now symptom scores at the end of the dosing interval showed a reduction of 24.3%, 25.3% and 17.7% for desloratadine 5 mg, desloratadine 7.5 mg and placebo, respectively. Similar improvements were observed in total nasal, total non-nasal and individual symptoms, as well as in physician and patient evaluation of therapeutic response and assessment of overall disease condition.

HQOL analysis in studies C98-223, C98-224 and C98-225 indicated that SAR produced a mild burden of disease. Improvements in subject-physician evaluations of clinical response to treatment were associated with improvements in HQOL.

Results from model #2 indicated a strong effect in favour of desloratadine (combined 5 and 7.5 mg dose groups) over placebo (p=0.003), and that there was no significant sex-by-treatment (p=0.30) or race-by-treatment (p=0.78) interactions.

An evaluation of the effect of age group on the treatment effect based on the pooled data was submitted in response to the List of Questions. Results showed that in the age group 12-18 years the clinical effect of desloratadine (pooled analysis 5 and 7.5 mg) shows only a numerical trend in favour of desloratadine but the sample size in this age group is not sufficient to demonstrate statistical significance.

Clinical studies in special populations

There were no studies in special populations.

Supportive studies

Four supportive studies (C98-226, I98-367, I98-448 and P00287) were performed to evaluate onset-of-action. In total 783 patients were included in these four studies out of which 508 received desloratadine.

Study C98-226

The primary objective of this study was to evaluate the onset of action of 5 mg desloratadine compared to placebo in the treatment of SAR exposed to pollen in an outdoor setting (July – September 1998). The placebo group in this setting had an unexpectedly high response with a reduction in total symptom score by 46% over the 5 hour study period compared to 51% reduction following 5 mg desloratadine. As there was no statistical difference between the active and placebo groups, the onset of effect could not be evaluated in this study.

Study I98-367

The primary objective of this study was to evaluate the onset of action of 5 or 7.5 mg desloratadine compared to placebo in the treatment of SAR exposed to ragweed pollen in an environmental exposure unit.

For the 5 mg desloratadine group the onset-of-action occurred at 2 h post-dose, based on analysis of the subject evaluated total symptom score excluding cough and at 3 h post-treatment based on analysis including cough. For the 7.5 mg group the onset-of-action occurred at 4 h post-treatment, irrespective

the inclusion or exclusion of cough in the analysis. Almost the same observations were done for the secondary efficacy parameters (e.g., subject evaluated total nasal symptom score, subject evaluated total non-nasal symptom score). Efficacy of the 5 mg dose occurred at 2h30 up to 3 h whilst efficacy of the 7.5 mg dose occurred at 1 to 1h30 later. Reduction of the individual symptom scores was even observed to occur somewhat later.

Study I98-448

The primary objective of this study was to evaluate the onset of action of 5 or 7.5 mg desloratadine compared to placebo in the treatment of SAR utilising the exposition to 1500 grass pollen grains / m^3 of air in the Vienna Challenge Chamber.

For the 5 mg desloratadine group the onset-of-action occurred at 1h15min post-dose, based on analysis of the subject evaluated total symptom score including or excluding cough. For the 7.5 mg desloratadine group the onset of action occurred at 3h30min post-treatment, irrespective of inclusion or exclusion of cough in the analysis. For the secondary efficacy parameters (e.g., subject evaluated total nasal symptom score, subject evaluated total non-nasal symptom score) onset of action occurred somewhat later. Again relief of symptoms was quicker in the 5 mg dose compared to the 7.5 mg dose.

Study P00287

The primary objective of this study was to evaluate the onset of action of 5mg desloratadine compared to placebo in the treatment of SAR utilising the exposition to 1500 grass pollen grains/m^3 of air in the Vienna Challenge Chamber.

Onset of action occurred at 1h45min post-dose, based on analysis of the subject evaluated total symptom score. For the secondary efficacy parameters a) subject evaluated total nasal symptom score and b) subject evaluated total non-nasal symptom score) onset of action occurred at 1h45min and 3h respectively. For the subject-evaluated therapeutic response the first statistically significant difference versus placebo was observed at 2h post-dose.

Discussion on efficacy

The data provided support the claim that doses of 5 mg or 7.5 mg are effective in reducing symptoms of Seasonal Allergic Rhinitis as compared to placebo. The claim is backed by the pattern of responses in the four multiple-dose, double-blind, placebo controlled and parallel group trials. The results are corroborated by a pooled analysis of the four trials, which showed desloratadine 5 and 7.5 mg to be superior to placebo and the effect of the two desloratadine doses not to be significantly different.

In the dose-ranging study the reduction of symptom scores was restricted to 28% from baseline. The limited reduction in symptom scores is also seen in the other three multidose trials. The mean change following desloratadine 5 and 7.5 mg might be statistically significantly higher than following placebo, but the numerical difference is small. In response to the List of Questions concerning the magnitude of effect of desloratadine the applicant explained that the mean change from baseline in the primary efficacy parameter of Total Symptom Score was relatively consistent across the 4 clinical efficacy trials, ranging from -4.2 (-24.6%) to -5.1 (-30.2%) units. On the other hand, the mean change from baseline in Total Symptom Score for the placebo group was more variable, ranging from -2.5 (-12.5%) to -3.9 (-21.7%). The variability and magnitude of the placebo response is difficult to explain, although it is likely due to variability in regional pollen counts.

To confirm that the magnitude of improvement in SAR symptoms observed is consistent with the expected response for an antihistamine in this disease state, the applicant compared the differences (delta) in mean reduction in symptom scores between desloratadine and placebo with those reported in recent publications for other antihistamines. The magnitude of the clinical effect following administration of 5.0 mg desloratadine was seen to be comparable to that published for other antihistamines that are currently used in medical practice. However, it seems from the percentage of improvement in Total Symptom Score that the clinical efficacy of 5 mg desloratadine is probably not superior to 10 mg loratadine.

The applicant had received scientific advice on the duration of the clinical studies from the CPMP in 1998, stating that in general, studies testing the efficacy of a medicinal product in SAR last 2 to 12 weeks, with duration of 4 to 6 weeks in most of the studies. The applicant was therefore asked to

explain the duration of 2-4 weeks studies with desloratadine. The applicant explained that the available patient population is actually not reliably symptomatic (for the purposes of an efficacy clinical trial) for more than 2-4 weeks. This is due to the variable duration of the pollen season and the variability in the onset of at least moderate symptoms in individual SAR patients. For a valid efficacy comparison vs. placebo, it is important to assure that the patients have the opportunity to exhibit significant SAR symptoms throughout the duration of the study. In addition, a review of the literature was conducted through a Medline search from 1985-1999. The search conditions were studies of SAR in which efficacy was assessed in subjects over 12 years of age, using only oral antihistamines, in a double-blind, placebo controlled fashion. This search yielded 26 publications, out of which 5 had a duration of 28 days or more. In the publications reporting studies over 2 weeks in duration, the efficacy of placebo increases over time, leading to a progressive decrease in the difference between the active treatment and the placebo groups. This increase in placebo response may be due to varying pollen counts over time. Therefore, with longer study duration, the likelihood increases that study subjects on placebo groups (as well as those receiving desloratadine) will experience a significant amount of days without being exposed to the pollen that triggers their symptoms. Furthermore subjects were required in all studies to be experiencing moderate to severe symptoms at study screening and baseline. This likely led to subjects being enrolled at the peak of their exposure to the pollen they were sensitised to. This peak will not last for 4 weeks. Therefore, subjects in the placebo groups (as well as those receiving desloratadine) were very likely exposed to a progressively decreasing amount of pollen throughout the study. This was considered to be an acceptable explanation for the short duration of the clinical trials.

In the List of Questions the applicant was asked to explain the influence of the seasons the studies were conducted in and the possible influence of mould spores. C98-001 was conducted in the spring season in the US, whereas C98223, C98-224 and C98225 had been conducted in the autumn season in US. In the spring tree pollens are followed in the early summer by grass pollen, which is similar to Europe. In the autumn the trees and grasses also pollinate in the southern states of the US, in other areas ragweed and other weed pollens are present. This autumn pollination pattern is also similar to that of many areas in Europe, where mugwort and ragweed are the major autumn pollen allergens. The pollen counts between C98-001 and C98-223, C98-224 and C98-225 were different, as these studies were conducted in different seasons. The mould levels in both seasons, though, were similar. However, the presence of mould and/or other inhaled allergens in patients screened for the study was neither an inclusion nor an exclusion parameter assessed in these trials. The subjects enrolled in C98001/223/224/225 were required at entry to be actively symptomatic, and to be allergic to an allergen that was pollinating at the time of the study (either tree, grass or weed pollen). There are data in the literature showing that the mechanism of action and symptoms of SAR are similar whether patients are sensitised to grass/tree or to ragweed pollens. Therefore, treatment of SAR during the spring or autumn should lead to similar conclusions with regards to the efficacy and safety of a compound. Furthermore the data provided in the response to the List of Questions showed that there was no direct correlation observed between pollen counts and symptom severity in the four studies.

The three onset of action studies utilising controlled-exposure chambers showed that the subjects first became aware of significant improvement in their SAR symptoms as early as 1 hour 15 minutes and up to 2 hours following desloratadine 5 mg. Both studies that evaluated desloratadine 7.5 mg determined the onset of action as 3 hours 30 minutes. The reason why the 7.5 mg dose had an apparently longer onset of action than the 5.0 mg dose is not clear.

As part of the List of Questions the applicant submitted the results of a study conducted in the Vienna Challenge Chamber (VCC) assessed the onset of action of desloratadine 5 mg in 28 subjects allergic to grass pollen. The study employed an open-label, noncomparative design in which subjects received a single dose of desloratadine 5 mg during exposure to grass pollen in the VCC. Onset of action was defined, as the first time point at which there was at least a 25% reduction from baseline in the Total Symptom Score. On the basis of this definition, the median time to onset was 48.5 minutes, with a 95% confidence interval of (38.0, 59.0). Although this was an open-label study, the results obtained are consistent with the 75-minute onset time obtained in I98-448, which was also conducted in the VCC. In conclusion, the onset of action for desloratadine has been demonstrated to occur from 1 to 2 hours after administration.

Clinical efficacy in Allergic Rhinitis (AR)

The clinical program to justify the efficacy and safety of 5 mg desloratadine tablets in subjects with AR included the SAR studies submitted in the initial Marketing Authorisation Application, two studies in patients with SAR and concomitant asthma and two studies in patients with Perennial Allergic Rhinitis.

Clinical Studies Conducted With Desloratadine					
Study No/Title.	Design	Objective	Treatments/ Dosing	Treatment Duration	Subjects/ Sex/age range
SAR studies (all included in initial MAA)					
C98-001	Randomised, double-blind, parallel groups	Safety and efficacy	2.5, 5.0, 7.5, 10 and 20 mg DL once daily vs placebo once daily	2 weeks	423 male/ 613 female 12-75 years
C98-223	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 and 7.5 mg DL once daily vs placebo once daily	2 weeks	181 male/ 315 female 12-72 years
C98-224	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 and 7.5 mg DL once daily vs placebo once daily	2 weeks	168 male/ 324 female 12-73 years
C98-225	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 and 7.5 mg DL once daily vs placebo once daily	4 weeks	162 male/ 313 female 12-75 years
PAR studies					
P00218	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 mg DL once daily vs placebo once daily	4 weeks	199 males/ 477 females 11-79 years
P00219	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 mg DL once daily vs placebo once daily	4 weeks	232 males/ 466 females 12-80 years
SAR/Asthma studies					
P00214	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 mg DL once daily vs placebo vs 10 mg montelukast	4 weeks	171 males/ 330 females 15-75 years
P00215	Randomised, double-blind, parallel groups	Safety and efficacy	5.0 mg DL once daily vs placebo vs 10 mg montelukast	4 weeks	166 males/ 257 females 15-68 years

A total of 4,797 subjects were evaluated in these studies, of which 1,655 subjects were treated with 5 mg desloratadine once daily.

The desloratadine clinical program was designed and conducted in accordance with relevant Good Clinical Practice and ICH guidelines regarding study conduct, record keeping, data collection and regulatory submission and under the principles of the Declaration of Helsinki (1996).

Subjects were required to have at least a two-year history of AR. They were also required to have had a positive skin test (prick or intradermal) response to an appropriate allergen within the 12 months prior to Screening. Subjects in all studies were to be clinically symptomatic at the Screening visit. Demographics at Baseline were similar across treatment groups. The subject population in this clinical program was generally representative of the overall demographics of allergy patients. Most subjects were between the ages of 18 and 64 years (87% in each treatment group) and Caucasian (≥78%); 66% of subjects in each treatment group were female.

In the MAH's response to the Request for Supplementary Information it was clarified that subjects at baseline were required to have a minimum average score in the mild to moderate range (11 (SAR) and 10 (PAR) out of 24 points). The subjects included did, however, have a higher mean baseline score (12.6-16.8 out of 24 points) corresponding to 36.2% having moderate to severe symptoms. The mean change in total symptoms score from baseline was analysed separately for the subgroups of patients with baseline total symptom score in the upper third of the severity scale. The treatment differences for these subgroups were representative of the results for all patients. It is therefore acceptable that the use of desloratadine is not restricted to subjects with mild to moderate allergic rhinitis.

Justification of Dosage Regimen

The justification for a DL 5 mg once daily dose selection in the treatment of SAR was summarised in the initial SAR Marketing Authorisation application. The DL 5 mg dose is justified for the treatment of allergic rhinitis, based on the significant overlap between SAR and PAR and the demonstration of equivalent exposure between DL 5 mg and loratadine 10 mg (as described in the SAR MAA).

Efficacy Endpoints

Efficacy results of the prespecified, protocol-defined primary and secondary efficacy variables from the eight studies are summarised separately. Slight differences between the SAR and PAR studies preclude an appropriate pooling of the primary endpoints. However, a pooled analysis of the six SAR and two PAR studies was carried out using a sum of the four common nasal symptoms (nasal discharge, nasal itching, sneezing, and congestion). The purpose of this additional analysis was to derive an overall estimate of the treatment effect.

Subjects self-evaluated their PAR and SAR symptoms twice each day (am, before dosing, and approximately 12 hours later in the pm) with both reflective (prior 12 hours) and instantaneous (now) scores. The symptoms of PAR and SAR were assessed daily by the subjects, and recorded in their diaries using a four-point scale: none (0), mild (1), moderate (2), and severe (3).

The primary efficacy variable for **SAR** and the primary time point in the SAR studies is defined in the section 'Clinical efficacy in seasonal allergic rhinitis'.

The primary efficacy variable for **PAR** (P00218 and P00219) was the average am/pm *instantaneous (now)* total symptom score, excluding congestion.

· **Nasal**: nasal discharge, postnasal drip, nasal congestion, nasal itching, and sneezing.
· **Non-Nasal**: itching/burning eyes, tearing/watering eyes, and itching of ears/palate.

The primary time point was the change from Baseline in average score over four weeks.
Although patients in the PAR studies rated nasal congestion severity twice daily along with the seven other symptoms, the nasal congestion symptom score was not included in the primary endpoint. This consideration was based on the allowance of pseudoephedrine rescue medication in these studies and guidance issued from the FDA on clinical development programs for drug products in allergic rhinitis.

The instantaneous evaluation of symptoms was chosen as the basis for the primary endpoint because PAR symptoms are generally understood to be subtler compared to SAR, and it was felt the instantaneous symptom score would more accurately capture treatment effect. Clinical considerations served as the basis to evaluate rhinorrhea by capturing symptoms scores on both anterior and posterior nasal discharge (nasal discharge and postnasal drip, respectively). The decision not to evaluate the non-nasal symptom of eye redness was also based on clinical consideration since eye redness is less pronounced in PAR compared to SAR.

Allergic rhinitis, by precise definition, refers only too nasal symptoms. However, the term is commonly used to include both nasal and non-nasal symptoms, even though the non-nasal symptoms are less pronounced in PAR.

In all AR studies, the secondary variables included change from Baseline in total nasal, total non-nasal, and individual symptom scores for the 12-hour prior and now average am/pm assessments, as well as at the separate am and pm time points. For all studies, global variables included the Overall Condition of Disease expressed as a change from Baseline, and an Evaluation of Therapeutic Response, expressed as a raw score.

Statistical Evaluation

The primary variable at the designated time point (Days 1-15 or Days 1-29) was analysed for each study using a two-way analysis of variance (ANOVA) that extracted sources of variation due to treatment and centre. All pair-wise comparisons were made at the two-sided 5% level of significance using the least squares means from the ANOVA. No adjustments for multiple comparisons were made in the four SAR studies because the test for statistical significance was performed using a dose-trend test. In the SAR/Asthma studies, no adjustments for multiple comparisons were made because a stepwise procedure was employed.

For all studies included in this dossier, efficacy results was presented for only the 5-mg DL vs. placebo comparisons.

All analyses of efficacy were based on all randomised subjects who had Baseline and some post-baseline efficacy data for a given efficacy variable (Intent-To-Treat principle).

A pooled analysis of the six SAR and two PAR studies was carried out using the four common nasal symptoms (nasal discharge, nasal itching, sneezing, and congestion) evaluated across all eight studies referred to as the *Common Total Nasal Symptom Score.* The sum of common nasal symptom scores was analysed for the mean of the first two weeks for all eight studies, and the mean of four weeks for the five studies with four weeks of data (Studies C98-225, P00214, P00215, P00218 and P00219).

A mixed-effect model was used to derive an overall estimate of treatment effect including treatment as a fixed effect and study as a random effect. The treatment-by-study interaction was included in the model. In addition, each study was allowed its own estimate of variance in the model.

Results Primary Efficacy Endpoint

The results of the primary efficacy variable for the PAR studies (i.e., change in average am/pm now total symptoms score excluding congestion) from all eight studies are summarised in the table below.

Total Allergic Rhinitis Symptom Score AM/PM Now average (excluding congestion)

Treatment group	Baseline		**Day 1-15 (Change from baseline)[a,b]**				**Day 1-29 (Change from baseline) [a,b]**			
	(n)	(mean)	(n)	(mean)	(%)	(p-value)	(n)	(mean)	(%)	(p-value)
C98-001		**SAR[c]**								
5 mg	171	12.0	171	-3.6	-28.3	<0.01	-	-	-	-
Placebo	173	11.7	173	-2.1	-12.0		-	-	-	-
C98-223		**SAR[c]**								
5 mg	165	14.1	165	-4.0	-28.1	0.04	-	-	-	-
Placebo	165	14.0	164	-3.1	-22.2		-	-	-	-
C98-224		**SAR[c]**								
5 mg	164	14.4	164	-4.3	-29.8	0.01	-	-	-	-
Placebo	163	14.7	161	-3.2	-20.6		-	-	-	-
C98-225		**SAR[c]**								
5 mg	158	14.3	157	-3.5	-24.5	0.62	157	-3.9	-27.0	0.83
Placebo	158	14.5	158	-3.3	-22.8		158	-3.8	-26.2	
P00218		**PAR[d]**								
5 mg	337	10.7	337	-3.5	-31.7	<0.01	337	-3.7	-35.0	<0.01
Placebo	337	10.6	337	-2.6	-24.4		337	-3.0	-27.4	
P00219		**PAR[d]**								
5 mg	346	10.3	346	-3.0	-28.4	0.86	346	-3.3	-31.1	0.49
Placebo	349	11.0	349	-3.0	-26.3		349	-3.5	-30.9	
P00214		**SAR/Asthma[c]**								
5 mg	166	12.4	166	-3.7	-29.3	<0.01	166	-4.2	-32.6	<0.01
Placebo	160	12.5	160	-2.2	-19.3		160	-2.9	-24.2	
P00215		**SAR/Asthma[c]**								
5 mg	140	13.5	140	-3.7	-26.2	0.02	140	-4.2	-30.0	0.04
Placebo	138	13.3	138	-2.6	-17.7		138	-3.3	-23.0	

a: Days 1-15 and 1-29 interval data inclue PM data from Day 1 and AM and PM data for other days.
b: Means are LS means from the ANOVA model with treatment and centre effects. Percentages are raw means.
c: TOTAL SAR symptom score was the sum of 7 individual symptom scores – 3 nasal (rhinorrhea, nasal itching, and sneezing) and 4 non-nasal (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate)
d: TOTAL PAR symptom score was the sum of 7 individual symptom scores – 4 nasal (rhinorrhea,postnasal drip/drainage, nasal itching, and sneezing) and 3 non nasal (itching/burning eyes, tearing/watering eyes, and itching of ears or palate)

The data are consistent with the clinical descriptions of PAR and SAR, where SAR patients exhibit more dramatic symptoms of AR (e.g., sneezing, itching, runny nose, etc) compared to PAR patients. Baseline scores were comparable between treatment groups in all studies except PAR Study P00219 in which the baseline symptoms scores of the placebo group were almost one point higher than that of the DL-treated group. This difference was statistically different (p=0.002). A correction for Baseline imbalance in total symptom scores using an ANCOVA did not change the results from non-significant

to significant, although numerical superiority was in favour of DL (in the ANCOVA, Days 1-15 DL= -3.19, placebo=-2.91, p=0.223; Days 1-29 DL=-3.49, placebo=-3.40, p=0.72), by contrast to the uncorrected analysis in which there was no numerical difference (Days 1-15), or the numerical superiority favoured placebo (Day 1-29).

Overall, the 5-mg DL dose was superior to placebo with respect to Days 1-15 average am/pm now symptom assessments in 6 of 8 studies (SAR Studies: C98-001, C98-223, C98-224, P00214, P00215 and PAR Study P00218). Reduction in Days 1-15 am/pm now total symptom score (average, excluding congestion) was significantly ($p \leq 0.04$) greater in the 5-mg DL group vs. placebo. A numerical advantage over placebo was found for the 5-mg DL group in SAR Study C98-225. No numerical advantage was observed in PAR Study P00219. Across all studies, total symptom reductions averaged 24.5%-32% in the 5-mg DL groups compared with 12%-26% in the placebo groups.

In 3 of 5 four-week studies (P00218, P00214 and P00215), reductions in Days 1-29 am/pm now total symptom score (average, excluding congestion) were significantly greater ($p \leq 0.04$) in the 5-mg DL group vs. placebo.

Analyses of am/pm now total symptoms score results including congestion produced results similar to those shown in the table above.

Confirmatory analyses of the am/pm prior total symptom scores excluding and including congestion was performed for all studies. The results were consistent with those presented above in the table above. At the Day 1-15 time point (the primary endpoint in the SAR studies), total symptom reductions, whether including or excluding congestion, were significantly greater ($p \leq 0.05$) in the 5-mg DL group than in the placebo group in 6 of 8 studies (SAR Studies: C98-001, C98-223, C98-224, P00214, P00125, and PAR Study P00128). Similar to the am/pm now data statistical significance for am/pm prior total symptom score was not reached in SAR Study C98-225, although a numerical advantage over placebo was demonstrated. No numerical advantage was observed in PAR Study P00219.

In summary, results of Days 1-15 average am/pm prior total symptom score analyses were consistent with those of the Days 1-15 average am/pm now symptom assessments. The results showed that the 5-mg DL dose was statistically superior to placebo for reduction in allergic rhinitis symptoms in 6 of 8 AR studies. These conclusions were not changed whether or not congestion was included as a symptom.

Results of pooled analysis

To measure the treatment effect of DL across the allergic rhinitis studies, a pooled efficacy analysis of the Common Total Nasal Symptom Score (sum of nasal discharge, nasal itch, sneezing, and congestion) for the 12-hour prior and now average am/pm assessments was performed. The results are shown in the tables below.

Mean change from baseline in average am/pm Prior Common Total Nasal Symptom Score

Endpoint	**Desloratadine**		**Placebo**		Delta	SEM	p-value
	N	Mean	N	Mean			
2 weeks	1646	-2.18	1639	-1.71	0.47	0.07	0.002
4 weeks	1146	-2.34	1142	-2.03	0.31	0.07	0.037

Mean change from baseline in average am/pm Now Common Total Nasal Symptom Score

Endpoint	**Desloratadine**		**Placebo**		Delta	SEM	p-value
	N	Mean	N	Mean			
2 weeks	1646	-1.88	1640	-1.48	0.40	0.06	0.002
4 weeks	1146	-2.11	1142	-1.84	0.28	0.09	0.086

An improvement in Common Total Nasal Symptom Score was seen across the two-week and four-week endpoints for the SAR and PAR studies; however, two studies, C98-225 and P00219, had

relatively small treatment effects. Overall, greater treatment effects are shown in the four-week studies at the two-week endpoint compared to the four-week endpoint.

The am/pm prior Common Total Nasal Symptom Scores show a statistically significant improvement for DL compared to placebo over both the two-week and four-week treatment periods. Similarly, the pooled analysis of am/pm now Common Total Nasal Symptom Scores from the eight studies show a statistically significant improvement for DL compared to placebo over the two-week treatment period and numerical improvement over the four week treatment period. The estimates of the treatment difference at both time-points support the overall efficacy of DL compared to placebo (15% to 27% of the placebo mean change from baseline). These pooled analyses confirm and support the results of the individual studies.

Results Secondary Efficacy Endpoints

Among the secondary efficacy measurements, am now total symptom score provides evidence of therapeutic effect at the end of the dosing interval. This is clinically relevant because nasal symptoms tend to be most troublesome in the early morning hours for many allergic rhinitis patients. Results are summarised below.

Total Allergic Rhinitis Symptom Score AM Now average (excluding congestion)

Treatment group	Baseline		**Day 1-15 (Change from baseline)[a]**				**Day 1-29 (Change from baseline)[a]**			
	(n)	(mean)	(n)	(mean)	(%)	(p-value)	(n)	(mean)	(%)	(p-value)
C98-001		**SAR[b]**								
5 mg	171	12.0	169	-3.3	-26.0	<0.01	-	-	-	-
Placebo	172	11.8	172	-2.1	-11.1		-	-	-	-
C98-223		**SAR[b]**								
5 mg	165	14.1	165	-3.8	-26.3	0.04	-	-	-	-
Placebo	165	14.0	163	-2.9	-19.7		-	-	-	-
C98-224		**SAR[b]**								
5 mg	164	14.3	164	-4.0	-27.6	0.03	-	-	-	-
Placebo	163	14.7	161	-3.0	-19.6		-	-	-	-
C98-225		**SAR[b]**								
5 mg	158	14.3	157	-3.2	-22.0	0.89	157	-3.5	-24.3	0.84
Placebo	158	14.5	158	-3.1	-21.4		158	-3.6	-25.0	
P00218		**PAR[c]**								
5 mg	337	10.7	337	-3.2	-29.4	0.01	337	-3.5	-32.7	0.02
Placebo	337	10.8	337	-2.5	-22.1		337	-2.8	-25.3	
P00219		**PAR[c]**								
5 mg	346	10.3	346	-2.8	-26.0	0.88	346	-3.1	-28.8	0.34
Placebo	349	11.1	349	-2.9	-25.0		349	-3.4	-29.7	
P00214		**SAR/Asthma[b]**								
5 mg	166	12.5	166	-3.5	-28.2	<0.01	166	-4.0	-31.7	<0.01
Placebo	160	12.5	160	-1.9	-17.1		160	-2.6	-22.4	
P00215		**SAR/Asthma[b]**								
5 mg	140	13.5	140	-3.5	-24.6	0.03	140	-4.1	-28.8	0.05
Placebo	138	13.3	138	-2.5	-16.1		138	-3.2	-21.6	

a: Means are LS means from the ANOVA model with treatment and centre effects. Percentages are raw means.
b: TOTAL SAR symptom score was the sum of 7 individual symptom scores – 3 nasal (rhinorrhea, nasal itching, and sneezing) and 4 non-nasal (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate).
c: TOTAL PAR symptom score was the sum of 7 individual symptom scores – 4 nasal (rhinorrhea,postnasal drip/drainage, nasal itching, and sneezing) and 3 non nasal (itching/burning eyes, tearing/watering eyes, and itching of ears or palate)

Similar to the am/pm now and prior total symptom score, in 6 of 8 AR studies (SAR Studies C98-001, C98-223, C98-224, P00214, P00215, and PAR Study P00218), 5 mg DL was significantly more effective than placebo ($p \leq 0.04$) in reducing am now total symptom scores over the first two-weeks of treatment (Days 2-15). Across all studies, am now total symptom score reductions, whether including or excluding congestion at Days 2-15 averaged 21%-29% for 5 mg DL compared with 11%-25% for placebo. In Studies P00214, P00215 and P00218 significant improvements ($p \leq 0.05$) in am now total symptom scores were also observed over the entire four-week treatment period (Days 2-29). Total symptom score reductions at the Day 2-29 time-point, whether including or excluding congestion, averaged 23%-33% in the 5-mg DL groups compared with 21%-30% in the placebo groups.

The am now total symptom score analyses indicated that 5 mg DL was superior to placebo for symptom reduction 24 hours after dosing. Significant reductions of symptoms were observed in 6 of 8 AR studies. Improvement of symptoms was seen over both the two-week and four-week treatment periods. Corresponding results for total symptom score including congestion were consistent with results for am now total symptom score excluding congestion.

In summary, efficacy is maintained for the full 24-hour dosing interval using once-a-day dosing.

In all studies, results of additional AR variables, including assessment of total nasal, total non-nasal, and individual symptom scores were consistent with am/pm now and prior total symptom score results.

The investigator and subject jointly evaluated the Overall Condition of AR. Response was recorded on a scale of 0 (none) to 3 (severe). In all eight studies, DL was numerically more effective than placebo for improvement in Overall Condition of AR at the endpoint of each study.

The investigator and subject also jointly evaluated Therapeutic Response at each post-baseline visit by comparing the current severity of disease symptoms to Baseline. Response was recorded on a scale of 1 (complete relief) to 5 (treatment failure). In all eight studies, DL was numerically more effective than placebo for positive response to therapy. Significant improvements compared with placebo ($p \leq 0.05$) were seen in the DL 5-mg groups of SAR Studies C98-001, C98-224, and PAR Studies P00218 and P00219.

Discussion on clinical studies

In two out of five four week studies the effect of desloratadine was not superior to that of placebo measured by days 1-29 am/pm total symptom score (average excluding nasal congestion) and the treatment effects shown in the four week studies were greater at the two week endpoint than at the four week endpoint. In their response to the Request for Supplementary Information regarding a maintained effect over four weeks the MAH responded that efficacy evaluated by standard methodology of twice daily symptom assessment captured in diaries is most clearly seen at the early timepoints and that difficulty in consistently demonstrating efficacy in clinical studies in AR has been acknowledged in FDA guidance and in the ICH E10 document. Furthermore, in the three out of five studies in which desloratadine showed efficacy superior to placebo the reduction in total symptom score from baseline increased for each successive week of treatment, however, increases were also seen for the placebo treated patients, whereby the difference was diminished.

The CPMP questioned the clinical relevance of the findings as the therapeutic benefit (verum minus placebo) is limited especially days 16-29. In response the MAH submitted the findings of a responder analysis for nasal symptoms with a clinically meaningful improvement in response to desloratadine defined as a 25% or greater improvement in common total nasal symptoms score. Although a significant higher number of responders was found in the verum group, this was a pooled analysis of the SAR and PAR studies and the MAH was requested in a Follow-On Request for Supplementary Information to give the pooled analysis mean change from baseline in average am/pm now common total nasal symptom score for the PAR studies alone.

The MAH submitted the results of the pooled analysis of mean change from baseline in average Common Nasal Symptom Score am/pm now from the Perennial Allergic Rhinitis studies (P00218 and P00219), which are shown below.

Average Am/pm now Common Nasal Symptom Score for Perennial Allergic Rhinitis

Endpoint	**Desloratadine N=683**	**Placebo N=686**	Delta	p-value
	Mean	Mean		
2 weeks	-1.786	-1.537	0.249	0.009
4 weeks	-1.956	-1.754	0.202	0.044
P-values are based on an analysis of covariance extracting sources of variation due to treatment, site, and baseline covariate effects				

The reduction in average am/pm now Common Nasal Symptom Score seen with desloratadine was superior to that of placebo at both the 2 and 4 week endpoints (delta=0.249 and 0.202 and p=0.009 and 0.044, respectively).

The MAH carried out a responder analysis using the same definition as in their responses to the Request for Supplementary information (i.e. a clinically meaningful improvement in response to desloratadine was a 25% or greater improvement in common total nasal symptoms score).

The percentage of patients with ≥25% improvement was significantly larger for desloratadine treated patients compared to placebo at both 2 and 4 week endpoints (p=0.012 and p=0.018 respectively, based on the Cochran-Mantel Haenzel statistic, with corrects for study effect). Over half of the desloratadine patients experienced a ≥25% improvement at the 2 and 4 week endpoints (50.7% and 56.8%, respectively).

PAR is primarily a disorder manifested by chronic nasal symptoms (i.e nasal discharge, itching, sneezing and congestion). Thus, relief of troublesome nasal symptoms is of utmost importance to PAR sufferers. More than 50% of the desloratadine treated patients experienced a clinically meaningful and a statistically significant reduction in nasal symptoms over the 4 week study duration when compared to placebo.

Conclusion on clinical studies

The primary efficacy analyses of am/pm prior and am/pm now total symptom score demonstrated that DL 5 mg was superior to placebo for reduction in symptoms of AR in 6 of 8 studies (5 in SAR and 1 in PAR), including the two studies conducted in subjects with SAR and concurrent asthma. The results of the pooled analysis of the common nasal symptoms and the secondary efficacy variables are consistent with the results of the primary parameter. The results of the pooled PAR studies showed a reduction in the average am/pm now Common Total Nasal Symptom Score seen with desloratadine was superior to that of placebo at both week 2 and 4 and that more than 50% of the desloratadine treated patients experienced a clinically meaningful and a statistically significant reduction in nasal symptoms over the 4 week study duration when compared to placebo.

Syrup and oral lyophilisate

The Marketing Authorisation Holder applied through a Type II variation for the same extension of indication for Aerius 0.5 mg/ml syrup and Aerius 5 mg oral lyophilisate.

No new data were submitted. CPMP considered it acceptable based on the bioequivalence between the film-coated tablet and the syrup formulation and between the film-coated tablet and the oral lyophilisate. The allergic rhinitis indication was considered also to be applicable to the desloratadine 0.5 mg/ml syrup for adults and adolescents and the desloratadine 5 mg oral lyophilisate, as it will be administered using the same dosage as the film-coated tablets presentation and for the oral lyophilisate also to the same population.

The desloratadine 0.5 mg/ml syrup is also indicated for seasonal allergic rhinitis and chronic urticaria in children (2 years of age or over). As perennial rhinitis is a disease of childhood and the nature and course of allergic rhinitis as well as the activity of antihistamines are similar in children and adults, the CPMP considered the new extended indication allergic rhinitis to be acceptable also in the age range 2 to 12 years old.

Clinical efficacy in Chronic Idiopathic Urticaria (CIU)

The clinical efficacy and safety studies were conducted according to GCP. The design, dose, duration and number of patients and demographic characteristics of the patients are given below.

Clinical Studies Conducted With desloratadine in CIU					
Study No/Title.	Design	Objective	Treatments/ Dosing	Treatment Duration Blinding	Centres/ Subjects/ Sex/age
P00220: Efficacy and Safety in the treatment of Chronic Idiopathic Urticaria (CIU) subjects with SCH 34117	Placebo-Control Parallel Group	Efficacy and Safety	SCH 34117, 5 mg QD Placebo QD	6 weeks Double Blind	29/226 M 56; F 170 13-84 years
P00221: Efficacy and Safety in the Treatment of Chronic Idiopathic Urticaria (CIU) subjects with SCH 34117	Placebo-Control Parallel Group	Efficacy and Safety	SCH 34117, 5 mg QD Placebo QD	6 weeks Double Blind	29/190 M 48; F 142 12-79 years

The symptoms evaluated were pruritus, number and size of hives, total symptom score (sum of pruritus, number of hives and size of hives), interference with sleep and daily activities, overall condition and therapeutic response. The symptoms were scored twice daily in both a reflective or PRIOR (how the subject was feeling for the preceding 12 hours), and instantaneous or NOW (how the subject was feeling a the time of the assessment).

The primary efficacy endpoint in both studies was the change from baseline in the average reflective pruritus score (from the diary). The secondary parameters were instantaneous/prior pruritus score, total symptom score, number and size of hives, interference with sleep and daily activities, response to therapy and determination of overall condition.

Desloratadine treatment resulted in a mean change from baseline in the average reflective pruritus score that was statistically significantly ($p<0.001$) higher than for placebo.

Average pruritus score reduction in % from baseline (days 1- 8)		
	P00220	P00221
Desloratadine	47.9	56.0
Placebo	21.9	21.5

The mean score at baseline (for both treatment arms) was greater than two and reflects a moderate to severe baseline status. For desloratadine this was reduced to an average score of mild, while the mean score for the placebo-treated group remained closer to moderate.

The difference in the pruritus scores between desloratadine and placebo remained significantly different over the entire treatment period. Analyses of the change from Baseline in the average reflective pruritus score (from the diary) over the entire treatment period (Days 1-42) revealed statistically significant differences in both studies ($p<0.01$).

Desloratadine treatment resulted in a mean reduction in pruritus from Baseline of 56.9% and 65.3%, respectively, in the two studies compared to a mean reduction of 34.1% and 30.4%, respectively, in placebo treated subjects, measured over the entire treatment duration of 42 days.

The difference in the pruritus scores between desloratadine and placebo remained statistically significantly different at all evaluated time points (up to the entire treatment period of six weeks) in one study.

This significance was not maintained beyond four weeks in the other study due to the higher placebo response rate caused by the higher discontinuation rate in the placebo group. Endpoint analyses (analysis of last valid visit for each patient), which adjust for the differential discontinuation rate, revealed however that the difference between desloratadine and placebo was significant over the entire treatment period in both studies. The difference in these reductions was statistically significant in both studies ($p=0.004$ and $p<0.001$). The reduction in pruritus scores (at the end of the study) were 58.4%

and 67.5%, respectively, for the desloratadine treated subjects versus 40.4% and 33.5%, respectively, for the placebo treated subjects.

Average pruritus score reduction in % from baseline (days 1- 42)		
	P00220	P00221
Desloratadine	58.4 (56.9)	67.5 (65.3)
Placebo	40.4 (34.1)	33.5 (30.4)

Non-adjusted values are put between brackets.

There is evidence that patients with chronic idiopathic urticaria can be divided into 2 groups: those who do respond to antihistamines (approximately 85%) and those that are relatively resistant to antihistamines. These latter patients frequently require the addition of other drugs. Patients that were refractory to antihistamines were excluded from the two studies. This is reflected in the SPC section 5.1.

In the two clinical studies a total of 22 subjects was in the age range 12 to 17 years and 17 subjects were ≥65 years of age. Of these 13 adolescents and 8 geriatric subjects received desloratadine 5 mg. The results for these two groups and the age group 18-64 is given below.

Mean change from baseline in pruritus score AM/PM prior 12 hours (days 1- 8) (P00220, P00221)						
	Desloratadine		**Placebo**			
	N	**Mean change**	**N**	**Mean change**	**Delta**	**p-value**
12-17 year olds	13	-1.31	9	-0.42	0.89	
18-64 year olds	189	-1.13	188	-0.50	0.63	<0.01
65 years old and older	8	-0.85	9	-0.44	0.41	

Neither the numerically higher difference seen in the adolescents or the numerically lower difference seen in the ≥65 years group are clinically different from the effect seen in the 18 to 64 years population. The estimates of the treatment differences in these subgroups could be attributed to less than reliable estimates in the smaller sample sizes. As a result statistical inferential analysis was not performed for these subgroups. From the results observed in the CIU trials it can be concluded that the adolescent and geriatric patients treated for CIU should receive the same benefit from desloratadine 5 mg as subjects 18-64 years of age.

Total symptom score and number and size of hives

The difference between desloratadine in total symptom scores (sum of pruritus, number and sizeof hives) remained significantly different throughout the entire treatment period. Analyses of the change from Baseline in the average reflective total symptom score (sum of pruritus, number of hives and the size of the largest hive; maximum score 9) over the entire treatment period (Days 1-42) revealed statistically significant differences in both studies ($p<0.01$).

Desloratadine treatment resulted in a mean reduction in total symptom score from Baseline of 52.9% and 60.2%, respectively, in the two studies compared to a mean reduction of 33.9% and 27.8%, respectively, in placebo treated subjects, measured over the entire treatment duration of 42 days.

Instantaneous/prior pruritus score

The instantaneous pruritus score, the morning diaries and the evening diaries (both reflective and instantaneous) were analysed separately, with nearly identical results, supporting the efficacy of the once daily dosing regimen. In both studies, the response rates increased over time for both treatment groups. After Week 3 during the treatment, pruritus reduction with desloratadine was reported up to 75% (range 66-75%), compared to 59% (range 47-59%) for placebo with only a slight difference between the two individual studies. The dropout rate in the placebo group was close to 30%; the majority due to treatment failure (29 out of 35 subjects) while the dropout rate in the desloratadine treated group was only 15%.

Interference with sleep and daily activities

At day 8, desloratadine treatment had resulted in a mean improvement from baseline compared to placebo-treated subjects for interference with sleep as shown in table below. These differences are statistically significant with p-values of 0.007 and <0.001, respectively.

Reduction in interference with sleep in % from baseline (Days 1- 8)		
	P00220	P00221
Desloratadine	44	53
Placebo	14	18

At day 8, desloratadine treatment had resulted in a mean improvement from baseline compared to placebo-treated subjects for interference with daily activities as shown in the table below. These differences are statistically significant with p-values of 0.001 and <0.001, respectively.

Reduction interference with daily activities in % from baseline (Days 1- 8)		
	P00220	P00221
Desloratadine	47	50
Placebo	17	20

The mean scores at baseline for both variables (interference with sleep and interference with daily activities) and treatment arms (desloratadine and placebo) were ≥ 1.5 reflecting mild to moderate interference. For desloratadine, this was reduced to a less than mild average interference (<0.8), while the score for the placebo treated group remained more than mild (>1.30) for both variables.

Response to Therapy and Determination of Overall Condition

Results from the evaluation of overall condition (jointly assessed by the subject and the physician) showed statistically significant differences between desloratadine and placebo over all the time points evaluated. At the end of treatment analysis (six weeks), the overall condition for desloratadine was reduced from moderate-severe at baseline (score of ≥ 2.4 in both studies on a 0-3 scale) to mild (score of about 1.0) while the placebo group remained close to moderate with a score of 1.40 and 1.55, respectively. These differences at the end of the treatment period (Week 6) were statistically significant with a p-value of 0.003 in study No. P00220 and a p-value of <0.001 in study No. P00221.

Overall Condition at the End of the Treatment (Week 6) Compared to Baseline				
	P00220		P00221	
	Baseline	**Week 6**	**Baseline**	**Week 6**
Desloratadine	≥ 2.4	1.0	≥ 2.4	1.0
Placebo	≥ 2.4	1.4	≥ 2.4	1.55

Results from the evaluation of therapeutic response (jointly assessed by the subject and the physician) showed also statistically significant differences between desloratadine and placebo over all the time points evaluated (all p-values were ≤ 0.002). Evaluated time points were Day 4, Day 8, Day 15, Day 29, Day 42, and endpoint.

Therapeutic Response at Endpoint		
	P00220	P00221
Desloratadine	2.74	2.75
Placebo	3.62	3.76

The scores at endpoint for desloratadine were 2.74 and 2.75, respectively, reflecting a marked to moderate relief while the scores for placebo were 3.62 and 3.76, respectively, (slight relief). These differences at endpoint were statistically significant with a p-value of <0.001 in both studies.

Oral lyophilisate

Pharmacodynamics

No new pharmacodynamics data have been provided.

Pharmacokinetics

Two studies in healthy adult volunteers were carried out. Study P01216 compared the bioequivalence of the 5 mg DL tablet, 5 mg DL oral lyophilisate tablet and a 5 mg dose of the DL syrup. Study P01419 evaluated the effects of food and water administration on the bioavailability of DL and 3-OH DL from the oral lyophilisate tablet formulation.

Studies in Healthy Volunteers Included in the Desloratadine Syrup Clinical Pharmacology Program

Protocol No.	Study Description	Study Design/Dosage	Sex[a]	Age[b]	Race[c]
P01216	Bioequivalence/ bioavailability of DL tablet, oral lyophilisate and syrup	Open-label, single-dose, three-way crossover (5 mg DL tablet; 5 mg oral lyophilisate tablet and 5 mg DL syrup, after overnight fast)	12 F, 18 M	21-45	7C, 2B, 2A, 19H
P1419	Bioavailability of 5 mg oral lyophilisate with/without food and water	Open-label, single-dose, three-way crossover study (5 mg DL oral lyophilisate tablet with water, 5 mg DL oral lyophilisate tablet without water and 5 mg DL oral lyophilisate tablet following a high-caloric, high-fat meal)	4 F, 26 M	22-45 years	22C, 8B

a: Sex: M = male; F = female.

b: Age is in years.

c: Race: A= Asian, C = Caucasian, B = Black, H = Hispanic.

Both studies evaluating relative bioavailability/bioequivalence employed a randomised, crossover and open-label design. The single-dose design used in both studies complies with the recommendations outlined in the European CPMP Guideline for Investigation of Bioavailability and Bioequivalence for this type of formulation. For these studies, the pharmacokinetic parameters (Cmax and AUC) were subjected to statistical analysis using a crossover analysis of variance (ANOVA) model. The effects due to subject, period and treatment were extracted. Cmax and AUC values were log-transformed and the 90% confidence intervals (CI) for the mean difference between the treatments expressed as a percent of each treatment mean. The power to detect a 20% difference in treatment means for an α-level of 0.05 (two-tailed) was calculated using the pooled residual error and associated degrees of freedom from the ANOVA. This study design in combination with these statistical tests, are considered to be the standard for evaluating bioequivalence.

Plasma concentrations were analysed for DL and 3-OH DL using a validated liquid chromatographic-mass spectrometric method (LC/MS/MS) with a lower limit of quantitation of 0.025 ng/ml. All analyses of plasma samples were conducted at PPD-Richmond, VA. These methods have been validated for specificity, sensitivity, linearity and reproducibility.

Across the two studies, following administration of the oral lyophilisate 5 mg tablet, a DL Cmax value of approximately 2.0 ng/ml was achieved at a median Tmax ranging from 2-3 hours in a fasting state. Mean DL AUC(I) values for the oral lyophilisate formulation were approximately 40 ng·hr/ml. The mean Cmax for 3-OH DL was approximately 1.0 ng/ml achieved at a median Tmax which ranged from 4-6 hours. The mean AUC(I) values for 3-OH DL ranged from approximately 25-30 ng·hr/ml. These data were consistent with the data from the DL 5 mg tablet studies. The mean parameters for DL and 3-OH DL following administration of DL 5 mg oral lyophilisate and DL conventional tablets are summarized in the table below.

Mean (CV%) Pharmacokinetic Parameters Following Administration of 5 mg DL oral lyophilisate and 5 mg DL Tablet

Study		P01216 (n=28)	P01216 (n=29)	P01419 (n=30)
Parameter Mean (CV %)	Compound Measured (Fasted Condition)	5 mg DL Tablet (Fasting)	5 mg oral lyophilisate (Fasting With Water)	5 mg oral lyophilisate (Fasting With Water
Cmax (ng/ml)	DL	2.18(35)	1.99 (30)	1.84 (38)
	3-0H DL	1.08 (27)	1.03 (28)	0.85 (34)
Tmax (hr)	DL	2 (1.5-8)	3 (1-6)	2.5 (1-12)
	3-0H DL	6 (1.5-8)	6 (1.5-6)	4.0 (1.5-48)
AUC(I) (ng·hr/ml)	DL	40.3 (45)	39.4 (43)	41.7(76)
	3-0H DL	29.5 (27)	29.0 (29)	25.7 (25)
t½ (hr)	DL	21.6 (19)	22 (22)	23.8 (36)
	3-0H DL	32.6 (20)	32.2 (17)	42.1 (107)

The bioequivalence of the DL oral lyophilisate formulation relative to the DL syrup and tablet formulation was evaluated to assess the interchangeability of these three formulations (P01216). The 5 mg oral lyophilisate formulation was found to be bioequivalent to the 5 mg tablet formulation and 5 mg of syrup with respect to both DL and 3-OH DL.

Estimates of Bioequivalence and the 90% Confidence Intervals for the Log-Transformed Cmax AUC(tf) and AUC for DL and 3-OH DL in Healthy Volunteers Following Single Oral Administration of DL 5 mg Tablets, 5 mg oral lyophilisate or 5 mg Syrup (n=28)

Protocol No. P01216

Comparison		Relative Bioavailability (%)	90% Confidence Interval (%)
5 mg oral lyophilisate Versus 5 mg Tablet			
DL[a]			
5 mg oral lyophilisate/Tablet	AUC(I)	97.1	92-102
	Cmax	91.5	85-99
3-OH DL[a]			
5 mg oral lyophilisate/5 mg Tablet	AUC(I)	97.0	93-101
	Cmax	93.5	87-100
5 mg oral lyophilisate Versus 5 mg Syrup			
DL[a]			
5 mg oral lyophilisate/5 mg Syrup	AUC(I)	100.9	96-106
	Cmax	96.4	90-104
3-OH DL[a]			
5 mg oral lyophilisate/ 5 mg Syrup	AUC(I)	100.8	97-105
	Cmax	99.0	93-106

a: Balanced data only: AUC(tf), AUC(I) and Cmax values for Subjects Nos. 14 and 26 were not included in the statistical analysis (log-transformed) since they did not have data for all treatments.

Therefore the DL oral lyophilisate tablet is interchangeable with both the conventional DL tablets and DL syrup formulations.

The effect of food (a high-fat, high-caloric meal) and water on oral lyophilisate bioavailability was assessed in a three-way crossover design (Protocol No. P01419).

Estimates of Bioequivalence and the 90% Confidence Intervals for the Log-Transformed Cmax and AUC(I) for DL and 3-OH DL in Healthy Adult Volunteers After Single-Dose Oral Administration of DL oral lyophilisate Under Either Fasted (With or Without Water) or Fed Conditions

Protocol No. P01419

Comparison		Relative Bioavailability (%)	Confidence Interval (%)
DL			
Fed/Fasted with water	AUC(I)	99.4	96-103
	Cmax	87.4	82-93
Fed/Fasted without water	AUC(I)	97.3	94-101
	Cmax	84.3	79-90
Fasted without water/Fasted with water	AUC(I)	102	98-106
	Cmax	104	97-110
3-OH DL			
Fed/Fasted with water	AUC(I)	95.4	92-99
	Cmax	93.9	89-99
Fed/Fasted without water	AUC(I)	94.0	91-97
	Cmax	92.6	88-98
Fasted without water/Fasted with water	AUC(I)	101	98-105
	Cmax	101	96-107

For all comparisons, AUC and Cmax parameters met the 80-125% bioequivalence acceptance range outlined in the European CPMP Guideline for Investigation of Bioavailability and Bioequivalence, with the exception of the DL Cmax parameter when the fed and fasted without water condition are compared (90% CI 79-90%). However, this slightly lower Cmax value under the fed condition is not clinically meaningful. Therefore, food and water administration had no clinically significant effect on the bioavailability of DL or 3-OH DL from the oral lyophilisate tablet. These findings are expected since no food effect has been previously identified with DL.

Tmax is 2.5 hr for DL and 4 hr for 3-OH DL in fasted subjects (without or with water); in fed subjects these values are prolonged to 4 hr for DL and 6 hr for 3-OH DL. These data are given in section 5.2. of the SPC.

Clinical efficacy

No clinical efficacy studies have been performed with the present DL oral lyophilisate formulation. Since the bioavailability to the conventional DL tablet has been demonstrated and a complete program of clinical efficacy and safety data has been presented during the authorisation procedure for DL 5 mg film-coated tablets, the lack of clinical efficacy studies is acceptable for the present DL oral lyophilisate formulation.

Syrup

Clinical pharmacology

The pharmacokinetic properties of desloratadine syrup were investigated in healthy volunteers. The 6 studies enrolled a total of 120 subjects, comprising 30 subjects aged 19 to 45 and 90 paediatric subjects; 54 aged 6 to 11 years and 36 aged 2 to 5 years old. The studies were conducted in compliance with GCP.

Overview of pharmacokinetic studies is given in the table below:

Study number	Primary objective/variable	Design	Desloratadine dose/comparator	Study populations
P00213	Bioequivalence of desloratadine tablet and syrup; food effect on desloratadine syrup	Open-label, single dose, three-way cross-over	5 mg desloratadine tablet 5 mg desloratadine syrup after overnight fast or standardised breakfast	24 male, 6 female 19-45 years
P00270	Pharmacokinetic profile of 5 mg desloratadine syrup	Open-label, single dose	5 mg desloratadine syrup	10 male, 8 female 6-11 years
P01126	Pharmacokinetic profile of 2.5 mg desloratadine syrup	Open-label, single dose	2.5 mg desloratadine syrup	9 male, 9 female 6-11 years
C98-577	Pharmacokinetic profile of 7.5 mg desloratadine tablets	Open-label, single dose	7.5 mg desloratadine tablet	9 male, 9 female 6-11 years
P00225	Pharmacokinetic profile of 2.5 mg desloratadine syrup	Open-label, single dose	2.5 mg desloratadine syrup	12 male, 6 female 2-5 years
P01125	Pharmacokinetic profile of 1.25 mg desloratadine syrup	Open-label, single dose	1.25 mg desloratadine syrup	10 male, 8 female 2-5 years

Pharmacodynamics

No new pharmacodynamics data have been provided. The pharmacodynamic properties of desloratadine were evaluated in the Marketing Authorisation application for the desloratadine film-coated tablets for adults and adolescents. No differences in pharmacodynamic properties of desloratadine are anticipated in the paediatric population.

Pharmacokinetics

The bioequivalence of the desloratadine syrup formulation relative to the tablet was evaluated to assess the interchangeability of these 2 formulations. Bioequivalence in adults was demonstrated in Study P00213, which showed that oral administration of a 5.0 mg dose of desloratadine syrup (0.5 mg/ml) and a desloratadine 5.0 mg tablet were bioequivalent.

Estimates of Bioequivalence and the 90% Confidence Intervals for the Log-Transformed Cmax and AUC(I) for DL and 3-OH DL in Healthy **Adult** Volunteers Following Single-Dose Oral Administration of a DL 5.0 mg Tablet and DL 5.0 mg Syrup (0.5 mg/ml) Formulation Under Fasted or Fed Condition

Formulation (Condition)		Relative Bioavailability (%)	90 % Confidence Interval
		Desloratadine	
Syrup (fast)/**Tablet** (fast)	AUC(I)	95.4	84-108
	Cmax	92.5	84-102
Syrup (fed)/**Syrup** (fast)	AUC(I)	104	92-118
	Cmax	94.1	85-104
		3-OH Desloratadine	
Syrup (fast)/**Tablet** (fast)	AUC(I)	94.9	89-101
	Cmax	96.5	89-104
Syrup (fed)/**Syrup** (fast)	AUC(I)	101	95-108
	Cmax	87.2	81-94

According to the literature, rhinitis in children shares most of the clinical and therapeutic characteristics with rhinitis in adults. Therefore, in order to ensure that the same efficacy and safety is achieved in children as demonstrated with desloratadine in adults, the applicant evaluated the dose of desloratadine that would result in comparable desloratadine and 3-OH desloratadine exposure (AUC and C_{max}) in children. The mean pharmacokinetic parameters presented in the table below allow a comparison of the exposure across all studies in the syrup program.

In Vivo Study Data Summary

Study		P00213 (N = 30/ Treatment)	P01228 (N = 12)	P01228 (N = 24)	C98-577 (N = 18)	P00270 (N = 18)	P01126 (N = 18)	P00225 (N = 18)	P01125 (N = 18)
Parameter Mean (CV %)	Compound Measured (fasted condition)	5.0 mg (Tablet / Syrup) Adults	5.0 mg (Tablet) Adults	5.0 mg (Tablet) **12-17 years**	*7.5 mg (Tablet) 6-11 years*	*5.0 mg (Syrup)* ***6-11 years***	**2.5 mg** (Syrup) **6-11 years**	*2.5 mg (Syrup)* ***2-5 years***	**1.25 mg** (Syrup) **2-5 years**
C_{max} ng/ml	DL (syrup)	**2.30 (51)**				*5.30 (39)*	**2.23 (35)**	*5.36 (41)*	**2.68 (50)**
	3-0H DL (syrup)	**1.03 (38)**				*1.77 (57)*	**0.764 (54)**	*1.27 (61)*	**0.644 (49)**
	DL (tablet)	**2.44 (41)**	2.25 (25)	2.40 (36)	*7.04 (42)*				
	3-OH DL (tablet)	**1.06 (34)**	0.804 (36)	0.927 (29)	*1.63 (65)*				
t_{max} hr	DL (syrup)	**3.58 (45)**				*2.78 (73)*	**3.67 (79)**	*2.94 (79)*	**3.17 (63)**
	3-0H DL (syrup)	**4.73 (39)**				*4.00 (42)*	**4.44 (42)**	*4.44 (63)*	**4.89 (35)**
	DL (tablet)	**4.17 (50)**	3.63 (91)	2.81 (80)	*5.78 (54)*				
	3-OH DL (tablet)	**4.72 (41)**	5.42 (52)	5.92 (45)	*6.22 (50)*				
AUC(tf) ng·hr/ml	DL (syrup)	**46.2 (71)**				*101 (89)*	**48.6 (88)**	*98.6 (76)*	**42.0 (49)**
	3-0H DL (syrup)	**26.0 (28)**				*43.0 (45)*	**20.5 (50)**[a]	*33.7 (51)*	**17.3 (42)**
	DL (tablet)	**45.8 (44)**	61.7 (69)	52.7 (49)	*171 (75)*				
	3-OH DL (tablet)	**27.0 (25)**	24.9 (33)	32.9 (35)	*44.7 (59)*				
t½ hr	DL (syrup)	**24.0 (23)**[b]				18.6 (49)	**19.4 (61)**	18.7 (60)	**16.4 (55)**
	3-0H DL (syrup)	**30.7 (21)**				26.8 (43)	**28.1 (65)**[a]	28.4 (67)	**26.2 (78)**
	DL (tablet)	**22.3 (21)**	23.4 (61)	17.9 (15)	*19.3 (59)*				
	3-OH DL(tablet)	**31.8 (21)**	39.2 (94)	27.4 (18)	*28.9 (57)*				

a: n = 17, t½ could not be calculated for Subject No. 16.

b: t½ = 21(22) hours when the same blood sampling schemes are used in adults and paediatric subjects.

There was a high degree of variability expressed as percent coefficient of variation (%CV) associated with AUC(tf) values. Contributing to the parameter variability was the presence of some patients who were slow metabolisers in these studies. Slow metabolisers were defined as subjects with AUC (tf) 3-OH desloratadine to desloratadine ratios of less then 10%. In Studies P00225, P00270, P01125, and P01126 there were 2-3 slow metabolisers in each study, and in Study C98-577 there were 4 slow metabolisers. A similar number of slow metabolisers have been reported in previous studies conducted with desloratadine tablets in adults. No subjects were considered to be a slow metaboliser in Study P00213.

Differences in t½ were observed between adults and children. The mean $t_{½}$ of paediatric subjects across studies following single dose administration of desloratadine ranged between 16.4 to 19.4 hours, compared with 21 (22) hours in adults (based on the same blood sampling scheme in adults as in paediatric subjects). The difference (8-22%) was considered to be pharmacokinetically unimportant. The primary pharmacokinetic parameter, total body clearance, which is reduced in paediatric subjects, resulted in the requirement to reduce the dose in order to provide the same exposure (Cmax, AUC) as in adults.

In response to the List of Questions regarding the shorter $t_{½}$ in children compared to adults the applicant argued that fewer blood samples had been taken in the paediatric studies compared to the adults. When $t_{½}$ was computed for adults in study P00213 based on the same blood-sampling scheme as used in paediatric subjects $t_{½}$ was 21 (22) hours. In study P01216 in which the syrup formulation was also studied in adults, a $t_{½}$ of 17.9 (20) hours was observed. These data show that DL $t_{½}$ of the same order of magnitude has been observed in children and adults.

In order to make proper comparison of AUC(tf) between paediatric and adult subjects (P00213), the common desloratadine concentration-time points (0, 1, 2, 4, 8, 12, 24, 48, and 72 hours) were extracted from the individual studies and the AUC(tf) values were calculated. Since the comparisons are being made across studies and due to the presence of slow metabolisers in some studies, median AUC values as opposed to mean values were used to compare exposure across studies.

In subjects 2 to 5 and 6 to 11 years of age, a single 2.5 mg (P00225) and 5.0 mg (P00270) oral dose of desloratadine, respectively, resulted in median desloratadine and 3-OH desloratadine AUC (tf) values that were approximately 2-fold the desloratadine and 3-OH desloratadine exposure observed in adults (P00213) following a 5.0 mg desloratadine dose.

However, a 1.25 mg (P01125) and 2.5 mg (P01126) dose of desloratadine in subjects 2 to 5 and 6 to 11 years of age, respectively, resulted in median desloratadine and 3-OH desloratadine AUC(tf) values that were comparable to the exposure of desloratadine and 3-OH desloratadine observed in adults (P00213) following a 5.0 mg desloratadine dose.

Consistent with AUC(tf) results, desloratadine and 3-OH desloratadine Cmax values in subjects aged 2 to 5 years and 6 to 12 years, following a 2.5 mg and 5.0 mg dose of desloratadine syrup were increased in comparison to adults receiving a 5.0 mg desloratadine dose. Following administration of half the initial dose, Cmax values in each age group were comparable to those observed in adults receiving a 5.0 mg dose of desloratadine.

In response to the List of Questions regarding the lower AUC in children compared to adults the applicant compared AUC(I), a measure of exposure, for children and adults. Because desloratadine exhibits linear pharmacokinetics in adults and is assumed to exhibit linear pharmacokinetics in children, AUC(I) is equivalent to AUC at steady state and is related to half-life as described below:

AUC (I) = (Dose x F/Vd) x 1.44 x $t_{½}$ (where Vd/F = apparent volume of distribution, $t_{½}$ = terminal phase half-life).

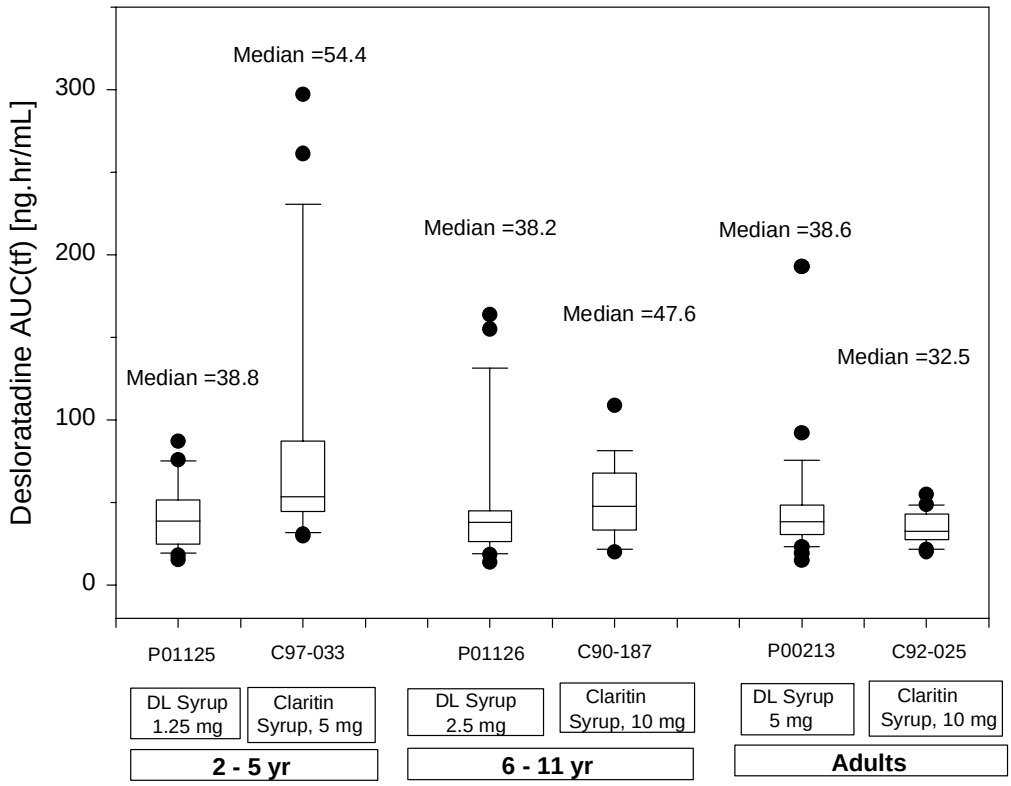
Differences between the AUC(I)s for the children (n=36) and adults (n=30) were evaluated by an unpaired t-test. There was no statistically significant difference (p=0.84) in the exposure between children and adults at their respective recommended doses.

In summary, a 1.25 mg and 2.5 mg dose of desloratadine syrup in paediatric subjects, aged 2 to 5 years and 6 to 11 years, respectively, provides desloratadine exposure comparable to the exposure observed in adults receiving desloratadine 5.0 mg tablets. The desloratadine 5.0 mg dose was proven efficacious in adult subjects with SAR and therefore paediatric subjects should have a therapeutic response at similar desloratadine exposure.

In addition, when median desloratadine exposure from loratadine syrup in children is compared to median desloratadine exposure from desloratadine syrup in the same age groups, these are shown to be comparable. This further supports the safety and efficacy of desloratadine syrup in children at the proposed dosage recommendations.

In the List of Outstanding Issues the CPMP questioned whether the doses proposed would result in sub-optimal efficacy in certain children. In response the MAH stated that on the basis of the clinical pharmacology studies conducted with DL syrup, it was determined that a 1.25 mg and 2.5 mg dose of DL in 2-5 and 6-11 year olds, respectively, matched the DL exposure produced by a 5 mg dose in adults. A 5 mg dose of DL syrup administered to adults results in a median $AUC_{(0\text{-}72\ hours)}$ of 35.3. This is comparable to a median $AUC_{(0\text{-}72\ hours)}$ of 38.7 in 2-5 year olds receiving 1.25 mg of DL syrup and a median $AUC_{(0\text{-}72\ hours)}$ of 38.4 in 6-11 year olds receiving 2.5 mg of DL syrup.

A graphic summary of the median DL $AUC_{(tf)}$ determinations from relevant clinical pharmacology studies performed with DL and loratadine syrup in adult and paediatric subjects is presented in the figure below.



Comparison of median desloratadine AUC values in paediatric and adult subjects administered desloratadine and loratadine syrup.

As shown in the figure above, the median DL $AUC_{(tf)}$ is essentially the same in paediatric subjects administered age-corrected doses of DL syrup and adult subjects administered DL 5 mg, and Importantly, these values are also similar to those in adults receiving 10 mg of loratadine syrup. The CPMP concluded that the proposed posology can be accepted as a variability towards a lower blood level has not been shown.

In Study P00213, it was demonstrated that food does not affect the pharmacokinetics of desloratadine or 3-OH desloratadine (according to PK analysis 3-OH desloratadine was also bioequivalent) following the administration of the desloratadine syrup formulation.

Clinical efficacy

No efficacy data have been submitted for this application. No efficacy data were recorded in the two Phase III safety studies with the syrup formulation. This is reflected in section 5.1 of the SPC.

Desloratadine 5.0 mg once daily was approved as a safe and effective dose for the treatment of SAR and CIU in adult and adolescent subjects. Pharmacokinetic studies have shown that the bioavailability of desloratadine from 5.0 mg desloratadine tablets and 10.0 mg loratadine tablets is essentially the same, with bioequivalent AUC (area-under-the-curve) values. Loratadine syrup (5.0 mg/5 ml or 10.0 mg/10 ml) has been shown to effectively reduce the symptoms of allergic rhinitis and allergic skin disorders in children 2 years of age and older.

Based upon the results of the clinical pharmacology paediatric studies, desloratadine 1.25 mg once daily and desloratadine 2.5 mg once daily administered using a syrup formulation were chosen as appropriate doses for subjects 2 to 5 years of age and 6 to 11 years of age, respectively.

Clinical safety

Film-coated tablet

Patient exposure in Seasonal Allergic Rhinitis

The total number of patients who has received desloratadine is 2,346; out of whom 1838 were included in the multiple dose studies and 508 in the onset of action studies.

The majority of the patients (93-98%) treated with 2.5, 5, 7.5, 10 and 20 mg were treated for 2 or more weeks. Only patients in study C98-225 were treated up to 4 weeks (139 subjects receiving 5 mg and 145 receiving 7.5 mg desloratadine.

The extent of exposure to desloratadine 5 mg is shown in the table:

	Number of subjects (N=659)				
Length of exposure	**C98-001**	**C98-223**	**C98-224**	**C98-225**	**Total**
≥ 1 dose	171	165	164	156	656
≥ 4 days	169	165	163	156	653
≥ 1 week	166	165	159	156	646
≥ 2 weeks	156	163	150	155	624
≥ 4 weeks	NA	NA	NA	139	139
Unknown	1	0	0	2	3
NA: not applicable					

Patient exposure in Allergic Rhinitis

A total of 3307 randomised subjects received either DL 5 mg (n=1655) or placebo (n=1652) in the eight allergic rhinitis studies. At least 83% of the subjects were treated for the protocol-specified length of time (2 or 4 weeks of dosing). The majority of subjects (about 65%) were treated for 3-4 weeks, with more than 90% of subjects treated for at least two weeks. Approximately 50% of subjects in the allergic rhinitis study groups (n=873 and 842 in the DL 5-mg and placebo groups, respectively) were treated for 29-35 days.

Patient exposure in Chronic Idiopathic Urticaria

All 211 subjects who were randomised and received the proposed clinical dose (5 mg QD) of desloratadine in the Phase III clinical program were evaluable for safety**.** The extent of exposure is shown in the table below.

Extent of Exposure to Treatment		
Length of Exposure	Desloratadine 5 mg QD (n=211)	Placebo QD (n=205)
1-7 days	211	205
8-14 days	202	178
15-21 days	192	159
22-28 days	181	150
29-35 days	177	146
36-42 days	176	138
43-49 days	132	108
≥ 50 days	7	1

Adverse events and serious adverse events/deaths

SAR studies

In the four multiple dose studies 43-49% of the subjects reported treatment emergent adverse events (TEAEs). Only 4-12% of the subjects reported TEAEs in the parallel group onset of action studies (C98-226 and I98-367) and no subjects reported TEAEs in the two crossover onset of action studies (I98-448 and P00287).

Most TEAEs were considered by the investigator unlikely to be related to treatment. The overall incidence of TEAEs considered by the investigator to be possibly or probably related to treatment was slightly higher in the groups treated with desloratadine (20% in the 2.5 mg group, 17% in the 5 mg group, 15% in the 7.5 mg group, 19% in the 10 mg group and 20% in the 20 mg group) than in the placebo group (13%). There was no evidence of a dose-related trend within the desloratadine groups.

The number of patients and the percentage of patients reporting the most frequently occurring TEAEs (≥2% of the subjects in any treatment group) are given below for the TEAEs in the multiple dose studies considered by the investigator to be possibly or probably related to the treatment.

Incidence of TEAEs reported by ≥2% of subjects by body system/Organ class (pooled data from the four multidose studies):

	Number (%) of patients	
	5 mg desloratadine (n=659)	**Placebo (n=661)**
No of subjects (%) with any related AE	111(17)	83(13)
Autonomic Nervous System	**21(3)**	**13(2)**
Mouth dry	21(3)	12(2)
Body as whole- general disorders	**56(8)**	**38(6)**
Fatigue	17(3)	10(2)
Headache	38(6)	26(4)
Central and peripheral Nervous System	**7(1)**	**6(<1)**
Dizziness	6(<1)	6(<1)
Gastro-Intestinal System Disorders	**9(1)**	**15(2)**
Nausea	4(<1)	5(<1)
Psychiatric System Disorders	**22(3)**	**20(3)**
Somnolence	14(2)	15(2)
Respiratory System Disorders	**17(3)**	**15(2)**
Epistaxis	3(<1)	4(<1)

The most common related TEAE with desloratadine 5 mg tablets was headache with 6% in subjects in the desloratadine groups and 4% in the placebo group. Other frequently reported TEAEs were dry mouth (3% for desloratadine, 2% for placebo), fatigue (3% for desloratadine, 2% for placebo) and somnolence (2% for both desloratadine and placebo).

Most of the AEs reported during the study were graded as mild to moderate in severity. The overall incidence of severe adverse events was similar among the treatment groups with 3-5% in the desloratadine groups and 3% in the placebo group. Headache was the most common related severe adverse event occurring in 2% of the subjects in the 5 and 7.5 mg groups and in 1% in the placebo group.

No life-threatening adverse events were observed and no deaths were reported during the study or within 30 days after the last dose of study medication.

Allergic rhinitis studies

A total of 16 serious adverse events occurred in 4,797 subjects treated in the AR studies (DL and placebo), or during the screening period for the AR studies. There were no reports of death or life-threatening adverse events. All serious adverse events were considered by the study investigators to be unlikely related to study drug.

Three of the 16 serious adverse events were unintended pregnancies. Although pregnancy does not meet the regulatory definition of a serious adverse event, pregnancy was for tracking purposes, captured as a serious adverse event in the clinical database. Two pregnancies occurred in placebo-treated subjects and 1 occurred during screening prior to study drug assignment. The thirteen serious

adverse events occurred in the following groups: 5 in DL, 3 in placebo, and 5 prior to study drug assignment (during the screening period).

The overall incidences of treatment-emergent adverse events (TEAEs) in the AR study groups were similar among the DL and placebo-treatment groups (about 40%). No unexpected adverse events were reported. Headache, which occurred at the same frequency in DL- and placebo-treated subjects (15%), was the only adverse event reported by ≥5% of subjects in the AR studies.

The overall incidences of treatment-related TEAEs in the AR studies were also similar among the two treatment groups (14% for DL and 12% for placebo). No related adverse event was reported by ≥5% of subjects. Headache (4%), dry mouth (2%-3%), somnolence (2%), and fatigue (1%-2%) were reported in similar proportions by the DL and placebo treatment groups.

The overall frequency and pattern of treatment-related TEAEs was similar among the individual clinical programs and consistent with the AR studies. The incidence of related TEAEs was also similar for DL and placebo within each allergic rhinitis subtype: SAR (DL 17% and placebo 13%), PAR (DL 11% and placebo 11%), and SAR/Asthma (DL 16% and placebo 14%).

In general, the overall incidence and pattern of adverse events in the pooled demographic subgroups (by age, race, and sex) were consistent with those observed in the overall study population.
The overall incidences of treatment-related adverse events seen in the AR pool are consistent with pooled analysis of safety data from 10 studies of DL 5 mg (the eight studies included in the AR pool and two studies in chronic idiopathic urticaria). Data from the 10 clinical studies were pooled for completeness and to provide a common description of the adverse event profile in the labelling across indications. Therefore Section 4.8 of the SPC reflects the pooled overall frequency of adverse events for DL 5 mg from these 10 studies.

No respiratory safety issues were identified for DL. The overall occurrence of TEAEs associated with the respiratory system in the pooled allergic rhinitis studies was similar between DL 5 mg and placebo (12% and 9%, respectively). There were no respiratory system safety issues identified in subjects randomised in the two four-week studies in subjects with SAR and concurrent asthma (P00214 and P00215).

Approximately 11% of subjects (in Studies P00214 and P00215) in each treatment group reported TEAEs associated with the respiratory system. The numbers of subjects reporting treatment-related TEAEs was low (≤4%) and comparable between the DL-, placebo- and montelukast-treatment groups (3.5%, 2.6%, and 2.3%, respectively).

CIU studies

In the two multiple dose studies in CIU the overall incidence of adverse events classified as being related to treatment with desloratadine was comparable to the incidence in subjects treated with placebo as seen in the table below.

Incidence of Treatment-Related Adverse Events Reported by ≥ 2% of Subjects in Either Treatment Group, by Body System/Organ Class (All Randomised Subjects)		
	DL 5.0 mg QD (n=211)	Placebo (n=205)
Any Treatment-Related Adverse Event [a]	**44 (20.9)**	**29 (14.1)**
Autonomic Nervous System Disorders	**8 (3.8)**	**6 (2.9)**
Mouth Dry	6 (2.8)	6 (2.9)
Body As a Whole – General Disorders	**19 (9.0)**	**8 (3.9)**
Fatigue	7 (3.3)	1 (<1)
Headache	12 (5.7)	8 (3.9)
Central and Peripheral Nervous System Disorders	**5 (2.4)**	**6 (2.9)**
Dizziness	5 (2.4)	4 (2.0)
Psychiatric Disorders	**7 (3.3)**	**8 (3.9)**
Somnolence	6 (2.8)	8 (3.9)
a: Number of subjects reporting treatment-related adverse events at least once during the study. Some subjects may have reported more than one adverse event.		

There were no deaths or life-threatening events in either study.

A total of 3 subjects (3/416) experienced serious adverse events during the period between signing of the informed consent till 30 days after completion of the treatment. One subject, treated with desloratadine, required hospitalisation for the removal of a kidney stone. One subject, treated with placebo, had a positive pregnancy test at the end of the study, and the third subject reported an anaphylactic reaction during the screening phase prior to randomisation. None of these events were considered to be related to the treatment.

Fatigue is the only treatment-related adverse event that was more frequently reported by the desloratadine treated subjects when compared to the placebo treated subjects (7 subjects vs. 1 subject). The apparent imbalance in this incidence was mostly a chance event occurring in a small number of subjects. Besides this, for the individual subject it might be difficult to discriminate between fatigue and somnolence. Interesting to note is that more subjects reported treatment related somnolence in the placebo group than in the desloratadine group (8 vs. 6 subjects). The most commonly reported treatment-related adverse event was headache, which occurred with a similar incidence in both treatment groups (12 subjects in the desloratadine treated group vs. eight in the placebo treated group).

All other treatment-related adverse events reported with desloratadine occurred to a similar extent with placebo. The severe treatment related adverse events occurred in <1% in both treatment groups. In fact, only two subjects in each treatment group reported a severe treatment related adverse event. The reported events in the desloratadine treated subjects were headache and fatigue versus headache and gastritis in the placebo treated subjects. None of these events resulted in study discontinuation.

Discontinuation due to adverse events in SAR studies

A total of 49 out of 2499 subjects (1838 treated with desloratadine and 661 with placebo) did not complete the studies due to adverse events (1-3% across the desloratadine groups and 2% in the placebo group). Most adverse events leading to discontinuation were due to concurrent illnesses frequently associated with SAR. There was no apparent pattern in the occurrence with respect to treatment group was seen. More than half of the patients (32/49, 65%) discontinued due to sinusitis, fatigue or headache.

Discontinuation due to adverse events in AR studies

Overall, between 2% and 3.6% of DL and placebo subjects in the allergic rhinitis studies discontinued due to adverse events. Most adverse events leading to study discontinuation were due to concurrent illnesses frequently associated with AR (e.g., sinusitis, upper respiratory tract infection, bronchitis, etc.). No single adverse event was related to study discontinuation in $\geq$1% of DL-or placebo-treated subjects. No subjects discontinued due to cardiovascular disorders or heart rate/rhythm disturbance. Two DL-treated subjects, both randomised in the SAR/Asthma studies, discontinued due to chest pain that was considered non-cardiac in origin.

Discontinuation due to adverse events in CIU studies

A total of ten (10/416) subjects discontinued the treatment due to treatment-emergent adverse events (6/211 in the desloratadine treated group vs. 4/205 in the placebo treated group). Most adverse events leading to study discontinuation were due to a concurrent illness (in six out of the ten subjects). The majority of these adverse events was of moderate severity (in nine out of the ten subjects) and was judged unlikely to be related to the therapy (in seven out of the ten subjects). None of the subjects discontinued from the study due to adverse events associated with heart rate/rhythm disorders.

A total of three subjects discontinued the treatment due to treatment related adverse events (1/211 in the desloratadine treated group vs. 2/205 in the placebo treated group).

The event causing discontinuation in the subject treated with desloratadine was nausea of moderate severity. The events causing discontinuation in the placebo treated subjects were vomiting and somnolence of moderate severity.

Laboratory findings

Clinical laboratory parameters

Clinical laboratory tests were carried out at screening and at endpoint in the eight multiple dose studies for AR and the two multiple dose studies in CIU. Median percent changes from baseline for all laboratory tests were evaluated. Overall only minimal changes were observed for all treatment groups and there was no apparent difference between the desloratadine treated groups and the placebo group.

The majority (≥ 81% for both desloratadine and placebo) in the AR studies had values within the normal range at baseline and at endpoint. Median percent changes in laboratory results, stratified by age, race, and sex showed no clinically relevant differences. There was no indication of a differential response to treatment between any of these sub-groups for any test, although some of the subgroups were too small for a robust analysis.

Vital signs

No change in any of the vital signs were observed in either AR or CIU studies that suggested a treatment effect. The proportion of patients with at least a 30% change from pretreatment values in blood pressure and heart rate was similar among treatment groups. Results of vital signs measurements stratified by age, race and sex showed, overall, no clinical relevant differences between treatment groups.

ECG-results in SAR studies

ECGs, including ventricular rate, PR, QR, QRS, QT, and QTc intervals, were evaluated at baseline and post-treatment. Overall, the majority of ECGs were observed to be normal at both screening and endpoint. Out of the 2469 subjects with both a baseline and an endpoint ECG, the investigators considered only 3 to have had a clinical meaningful abnormal ECG.

One patient treated with 5 mg desloratadine in C98-001 had a 7% increase in the QT_c interval (431 msec at baseline, 465 msec at visit 5) and an increase in heart rate from 57 bpm at screening to 63 bpm at endpoint. The changes were not accompanied by any clinical symptoms or cardiovascular adverse events. The second subject treated with 5 mg desloratadine in study C98-001 had a septal infarction at screening, which was clinically significant at endpoint. It was subsequently determined that the abnormalities seen at endpoint were identical to the ones seen at screening. The third person (7.5 mg desloratadine group in C98-223) had a clinically meaningful abnormal ECG at both screening and endpoint with a QT_c interval of 511msec at screening and 502 msec at endpoint. The patient was discontinued after 3 days treatment, as this was a protocol violation. No clinical symptoms apart from headache had been reported.

Mean percent changes in ECG interval data including ventricular rate, PR, QRS, QT and QT_c interval were evaluated. Overall there were no apparent differences between any of the treatment groups. A slight mean increase in ventricular rate was seen in the 20 mg desloratadine group (4.5 bpm) compared to the placebo group (0 bpm in C 98-001, 0.1 bpm in pooled data). The mean QT_c interval decreased by 1 to 4% in all the desloratadine groups and by 1% in the placebo group. For all treatment groups the percent change from screening was ≥-10% and <10% for the majority of subjects.

ECG-results in AR studies

The incidence and pattern of cardiovascular adverse events in the DL-treatment group was similar to that observed in the placebo group. This updated cardiac safety database includes data from additional 966 DL-treated and 991 placebo-treated subjects of which 74% were treated for at least 29 days.

The proportion of subjects with at least a 30% change from Baseline in blood pressure or heart rate at either visit was similar among treatment groups. The frequency of other cardiovascular events was similar with the exception of tachycardia, which occurred in three DL-treated subjects and no placebo-treated subjects. There were two reports of syncope in one placebo-treated subject and one montelukast-treated subject. No syncopal episodes occurred in DL-treated subjects.

The majority of ECGs were normal at both Baseline and Endpoint. No appreciable effects of DL treatment were observed on ECG intervals. In particular, no effects were observed on QTc intervals calculated by the Fridericia (FQTc) and Bazett (BQTc) formulae. Distribution data categorised as

percent changes from Baseline did not suggest a pharmacological effect for DL. There were no noteworthy differences among age, race, and sex subgroups.

One of 966 desloratadine subjects had clinically significant ECG changes. This subject had an ECG that was normal at Baseline, but was considered abnormal and clinically significant at Endpoint. This subject had a QTc value of 394 msec at Baseline that was prolonged at Endpoint (520 msec based on the Fridericia formula). These QTc values were consistent with those calculated using the Bazett formula. Although the ECG was of poor quality, a manual reread confirmed the prolongation of QTc at Endpoint. The prolonged QTc interval was not considered by the investigator to be an adverse event. The subject had a history of fluid retention.

ECG-results in CIU studies

Out of the 211 subjects in the clinical program who received desloratadine, no severe or serious adverse events related to the cardiovascular system were reported. No patients discontinued from the study due to cardiovascular events. One desloratadine-treated subject reported palpitations of moderate severity together with a severe fatigue resulting in interruption of the therapy. The subject discontinued from the study due to a treatment failure. The ECGs at screening and at the final visit were normal and the medical history for cardiovascular disorders was negative. Two other subjects reported a mild hypertension as an adverse event (one in each treatment group); both were considered to be unrelated to the treatment by the investigators.

ECGs, including ventricular rate, PR, QRS, QT, and QTc intervals were evaluated at screening and endpoint (post-treatment). Most electrocardiograms in the studies were normal at both time points. There were no apparent differences between the two treatment groups in ECG intervals (including the QTc intervals) and no noteworthy differences between males and females. The age or race subgroups were too small to draw definitive conclusions, however, there were no obvious differences between groups.

Safety in special populations

Hepatic impairment

No patients out of the 2346 desloratadine treated subjects reported an adverse event associated with the hepatic system.

Only 2 out of 1838 desloratadine-treated patients showed clinically meaningful elevations in hepatic enzyme levels. One subject in the 10mg desloratadine group of study C98-001 and 1 subject in the 7.5mg desloratadine group of study C98-223. They had normal AST values at screening (18 U/L and 34 U/L, respectively) and elevated values at endpoint (159 U/L and 155 U/L). In the former it was thought to result from the intake of creatinine powder, the latter subject refused to return for a repeat laboratory evaluation.

Study C98-354 compared the pharmacokinetics of a single dose of desloratadine 7.5 mg in subjects with normal liver function to subjects with various degrees of stable chronic liver disease. Namely, Pugh's Modification of Child's classification score 5 to 6 (n=4), score 7 to 9 (n=4), and score 10 to 15 (n=4). Subjects with hepatic dysfunction had mean AUC and Cmax values of desloratadine that were up to 2.4 times greater, respectively, than healthy subjects. However, there was considerably overlap of the AUC values of the 4 groups. There were no significant differences in the $t_{1/2}$ among subjects with hepatic dysfunction to that in normal subjects. Overall, 10 of 20 subjects reported TEAEs. The most frequently reported, regardless of severity of hepatic dysfunction, were headache and abdominal pain. The majority of the TEAEs were reported as being mild. Vital signs showed no consistent changes of clinical relevance.

In response to the List of Questions interim results were submitted from a multiple dose study (P00272) in subjects with hepatic impairment. The overall incidence of AEs was similar for desloratadine and 3-OH-desloratadine. AEs were reported in 5/11 subjects with moderate hepatic impairment and in 5/9 subjects with normal liver function. Headache was the most frequently reported AE (4/9), reported by subjects with normal liver function, while drowsiness was the frequent AE (2/11) in subjects with moderate hepatic impairment.

Renal

There were no noteworthy findings relevant to the renal system in any of the studies performed in the desloratadine clinical program in SAR. There was no evidence of any desloratadine-related effects on serum creatinine levels or on BUN levels in 1838 desloratadine-treated subjects in the multiple dose SAR studies.

Study C98-355 is comparing the pharmacokinetics of a single dose of 7.5mg desloratadine in subjects with normal renal function to subjects with various degrees of stable chronic renal insufficiency.

AEs were reported in 2/6 subjects each in the moderate, severe, and end-stage renal disease (hemodialysis-dependent) groups. No AEs were reported in subjects with normal renal function or in subjects with mild renal insufficiency. No AE was reported by more than 1 subject. One subject in the severe renal insufficiency group reported mildly increased liver function tests that were considered by the investigator to be possibly related to treatment.

There was no indication of an increase incidence of AEs with increasing renal impairment.

Discussion on clinical safety

Intake of H_1-receptor antagonists has been associated with a specific, potentially fatal polymorphic ventricular tachycardia termed torsade de pointes. This tachycardia is usually observed in the setting of a prolonged QTc interval, often initiated following extrasystolic pauses. In order to evaluate the cardiovascular properties of desloratadine the applicant has performed a separate cardiovascular safety evaluation. In addition, an analysis of the ECGs was conducted based on the CPMP guidelines for assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products was performed.

In response to the List of Questions the applicant submitted data according to QTc at baseline. The patients with normal QTc at baseline (n=2393, 96%) showed a comparable pattern for QTc-prolongation between drug and placebo without evidence for a dose response. No safety concerns were identified for patients who entered the studies with borderline baseline (n=87, 3.5%) and elevated baseline QTc-values (n=19, 0.8%). Neither in the patients with borderline baseline QTc nor in patients with elevated baseline QTc was any increase of >30 msec observed. Based on this, no evidence was found that desloratadine is associated with relevant QTc-prolongation, even in patients with borderline or abnormal baseline values.

To address the CPMP request to also consider individual values, the applicant submitted data on the shifts between the categories normal QTc, borderline QTc and prolonged QTc according to the CPMP-classification. The shift pattern between the categories of normal, borderline, or prolonged QTc of patients on desloratadine (2.5 to 20 mg) showed a random pattern without evidence of a drug effect. At the same time, the shifts were comparable to placebo.

There were no AEs that were reported by the "slow" metabolisers that were not reported by the “normal” metabolisers. Also, there were no serious AEs reported by the two groups. Overall, except for gastrointestinal AEs reported in “normal” metabolisers during co-administration of desloratadine and erythromycin, headache was the most frequently reported AE by both groups. At the 5 mg dose there is no difference in the percentage of subjects reporting AEs in the “slow” or “normal” metabolisers. No adverse events relating to the cardiovascular system were reported and the comparison of the electrocardiographic parameters for the “slow” and “normal” metabolisers showed no clinically relevant differences between the two groups. In summary the data shows that there are no clinically meaningful differences with respect to the AE profile of the "slow" versus the "normal" metaboliser.

Oral lyophilisate

Safety assessments for the 60 subject in the two studies P01216 and P01419 included adverse event evaluations, clinical laboratory tests, physical examinations, vitals signs, and electrocardiogram (ECG) measurements. Single dose administration of DL oral lyophilisate, syrup or conventional tablet was safe and well tolerated by most subjects. Most adverse events were mild to moderate in severity. The most commonly reported adverse event was headache, which occurred in 0-10% of subjects in each individual treatment group of both studies. No subjects in study P01216 experienced an adverse event

that was considered related to treatment and only one subject in study P01419 experienced an adverse event (headache) that was considered related to treatment.

There was one severe adverse event reported in study P01216. One subject, a 42-year-old male Caucasian, had elevated AST, ALT and LDH. The subject was discontinued from the trial, and a follow up laboratory examination on Day 21 demonstrated a resolution of these findings. These changes were not considered treatment-related.

One subject in study P01419 reported a severe headache on two separate occasions.

Based on the Clinical Pharmacology studies, the 5 mg DL oral lyophilisate tablet was found to be bioequivalent to the conventional 5 mg DL tablet formulation and 5 mg of DL syrup. Therefore, it is expected that the 5 mg oral lyophilisate formulation will have the same efficacy and safety profile of the 5 mg DL tablet. Additionally, the bioavailability of DL and 3-OH DL from the oral lyophilisate formulation was not affected by the concomitant administration of food or water. Therefore, the 5 mg oral lyophilisate formulation may be administered without regard to meals or water.

Syrup

In addition to the pharmacokinetic studies with desloratadine syrup in children, the paediatric safety of desloratadine was further evaluated in two phase III safety studies.

Study number	Primary objective/variable	Design	Desloratadine dose/comparator	Study populations
P00302	Phase III safety study of desloratadine in paediatric subjects, age 6 to 11 years with a history of allergic rhinitis or chronic idiopathic urticaria	Single-centre, randomised, double-blind, placebo-controlled, parallel-group	Desloratadine 2.5 mg once daily (60 subjects) versus placebo (60 subjects) for 15 days	52 males, 68 females 6-11 years
P00303	Phase III safety study of desloratadine in paediatric subjects, age 2 to 5 years with a history of allergic rhinitis or chronic idiopathic urticaria	Single-centre, randomised, double-blind, placebo-controlled, parallel-group	Desloratadine 1.25 mg once daily (55 subjects) versus placebo (56 subjects) for 15 days	62 males, 49 females 2-5 years

The studies were performed in accordance with Good Clinical Practice.

Desloratadine syrup was evaluated at a 1.25 mg dose in children 2 to 5 years of age and at a 2.5 mg dose in children 6 to 11 years of age. A total of 231 subjects received at least 1 dose of study drug and was evaluated for safety. Safety assessments included adverse event evaluations, clinical laboratory tests, physical examinations, vitals signs, and electrocardiogram (ECG) measurements.

Both genders and primarily Black (66%) and Caucasian (33%) races were represented in these studies. Similar to adults, the incidence of slow metabolisers (higher desloratadine exposure) is higher in Blacks compared to Caucasians. The safety profile in Blacks in this Phase-III paediatric clinical program was not different from the remainder of the population. Therefore, it can be concluded that the safety of desloratadine has been adequately evaluated for use in the paediatric population. The 2 to 5 year age group was stratified so that each year of age was adequately represented. The demographics of the patient populations enrolled in these trials were similar and the slight differences between treatment groups did not affect the results of these studies.

A summary of the demographic data for paediatric subjects with a documented history of allergic rhinitis or CIU, 2 to 5 years and 6 to 11 years of age, in the placebo-controlled studies (P00303 and P00302, respectively) is presented in the table below.

Summary of Demographic Data at Baseline (All Randomized Subjects)

	2 to 5 Years of Age [a]		6 to 11 Years of Age [b]	
Demographic Characteristics	DL 1.25 mg ONCE DAILY (N = 55)	Placebo (N = 56)	DL 2.5 mg ONCE DAILY (N = 60)	Placebo (N = 60)
Age (years)				
Mean (SD)	3.5 (1.26)	3.4 (1.17)	7.9 (1.51)	8.5 (1.67)
Median	4	3	8	9
Range (Min – Max)	2 - 5	2 - 5	6 – 11	6 – 11
Age Subgroup, n (%)				
2 to < 3 years	17 (31)	18 (32)	--	--
3 to < 4 years	10 (18)	11 (20)	--	--
4 to < 5 years	9 (16)	14 (25)	--	--
5 to < 6 years	19 (35)	13 (23)	--	--
6 to < 7 years	--	--	11 (18)	10 (17)
7 to < 8 years	--	--	17 (28)	10 (17)
8 to < 9 years	--	--	12 (20)	8 (13)
9 to < 10 years	--	--	9 (15)	13 (22)
10 to < 11 years	--	--	7 (12)	11 (18)
11 to < 12 years	--	--	4 (7)	8 (13)
Sex, n (%)				
Male	31 (56)	31 (55)	31 (52)	21 (35)
Female	24 (44)	25 (45)	29 (48)	39 (65)
Race, n (%)				
Caucasian	13 (24)	13 (23)	29 (48)	21 (35)
Black	42 (76)	42 (75)	30 (50)	38 (63)
Asian	0	0	1 (2)	0
Hispanic	0	1 (2)	0	1 (2)
Weight (Ib)				
Mean (SD)	39.2 (8.70)	38.5 (8.69)	72.0 (25.83)	74.7 (22.70)
Median	37.0	37.5	65.0	69.5
Range (Min - Max)	26 – 62	22 - 68	41 – 155	43 – 131
Height (in)				
Mean (SD)	40.7 (5.40)	40.2 (5.14)	51.6 (5.03)	53.1 (4.95)
Median	42.0	41.0	51.0	53.3
Range (Min - Max)	31 – 52	30 - 48	43 – 64	42 – 63

SD = Standard Deviation; Min = Minimum; Max = Maximum; lb = pound; in = inches.

a: Clinical Study Report P00303.

b: Clinical Study Report P00302.

All subjects in both studies completed their respective study. Two hundred and thirty subjects (all but one subject) completed at least 14 days of treatment with desloratadine syrup or placebo.

Adverse events

Adverse events reported in the paediatric clinical trials were noted on the diary card by the child's parents or guardian. When the child returns to the investigative site, events noted on the diary card, or mentioned by the parent/guardian, are discussed to determine the duration and severity of the event.

The overall incidence of adverse events was similar for the desloratadine and placebo groups (7.0% and 10.3%, respectively), as shown in the table below. Among the 6- to 11-year-old subjects, the incidence of adverse events was lower for subjects treated with desloratadine 2.5 mg (1.7% [1/60]) than for subjects treated with placebo (10.0% [6/60]). Among the 2- to 5-year old subjects, the

incidence of adverse events was similar for subjects treated with desloratadine 1.25 mg (12.7% [7/55]) and placebo (10.7% [6/56]).

Incidence of Treatment-Emergent Adverse Events by Body System/Organ Class and Treatment (All Randomized Subjects)

	Number (%) of Subjects [a]					
	2 to 5 years		6 to 11 years		Total	
Body System/Organ Class Preferred Term	DL 1.25 mg (N = 55)	Placebo (N = 56)	DL 2.5 mg (N = 60)	Placebo (N = 60)	DL (N = 115)	Placebo (N = 116)
Any Adverse Event[b]	**7 (12.7)**	**6 (10.7)**	**1 (1.7)**	**6 (10.0)**	**8 (7.0)**	**12 (10.3)**
Body As a Whole – General Disorders	**4 (7.3)**	**5 (8.9)**	**1 (1.7)**	**4 (6.7)**	**5 (4.3)**	**9 (7.8)**
Fever	3 (5.5)	3 (5.4)	0	0	3 (2.6)	3 (2.6)
Headache	1 (1.8)	3 (5.4)	1 (1.7)	4 (6.7)	2 (1.7)	7 (6.0)
Gastrointestinal System Disorders	**0**	**0**	**0**	**2 (3.3)**	**0**	**2 (1.7)**
Gastroenteritis	0	0	0	2 (3.3)	0	2 (1.7)
Vomiting	0	0	0	2 (3.3)	0	2 (1.7)
Resistance Mechanism Disorders	**3 (5.5)**	**2 (3.6)**	**0**	**0**	**3 (2.6)**	**2 (1.7)**
Infection, Viral	1 (1.8)	1 (1.8)	0	0	1 (<1.0)	1 (<1.0)
Otitis Media	0	1 (1.8)	0	0	0	1 (<1.0)
Varicella	2 (3.6)	0	0	0	2 (1.7)	0
Skin and Appendages Disorders	**1 (1.8)**	**0**	**0**	**0**	**1 (<1.0)**	**0**
Rash	1 (1.8)	0	0	0	1 (<1.0)	0
Urinary System Disorders	**2 (3.6)**	**0**	**0**	**0**	**2 (1.7)**	**0**
Urinary Tract Infection	2 (3.6)	0	0	0	2 (1.7)	0

a: Number of subjects reporting treatment-emergent adverse events at least once during the study. Some subjects may have reported more than 1 treatment-emergent adverse event.

b: Without regard to relationship to study drug.

The most common adverse events were headache (which was reported by less than 2% among subjects in each of the desloratadine groups and 5% to 7% of subjects in the placebo groups) and fever (which was only reported among desloratadine and placebo subjects in the 2- to 5-year-old group; 3 [< 6%] subjects each).

No adverse events categorised as general cardiovascular or heart rate and rhythm disorders were reported. In addition, there were no reports of dry mouth (a sensitive indicator of anticholinergic activity), somnolence, insomnia, fatigue, paradoxical excitability, or parakinesia.

With the exception of 1 report of moderate ear infection in the placebo group (2 to 5 years of age), all adverse events, regardless of age group or treatment, were mild in intensity.

Only 2 treatment-related adverse events were reported in the clinical program: 2 (3.6%) of the 55 subjects in the desloratadine 1.25 mg group had adverse events (1 report each of headache and rash) that the investigator considered possibly related to treatment. Both events were of mild intensity. Neither adverse event led to discontinuation. The subject that experienced the rash had a history of eczema on his arms, legs and feet since birth. The rash occurred on Day 11 and treatment was interrupted for 4 days. The subject was administered a dose of desloratadine syrup on the last day of treatment. No treatment-related adverse events were reported in the placebo group.

All treatment-emergent adverse events among the 6- to 11-year-old subjects who received either desloratadine 2.5 mg or placebo were not considered related to treatment.

No deaths or severe adverse events were reported and no subject discontinued study treatment.

A total of 6 subjects had treatment interrupted. One subject in the 2- to 5-year old group had treatment with desloratadine 1.25 mg interrupted for 4 days due to an adverse event (rash; see above). Two subjects in the 6- to 11-year-old group had placebo treatment interrupted for 1 day each because of adverse events (both subjects reporting both gastroenteritis and vomiting).

In addition, 3 subjects in the 2- to 5-year old group each missed 1 dose of study drug: 2 subjects in the desloratadine 1.25 mg group because of chicken pox and 1 subject in the placebo group because of dental work.

There were no apparent trends in adverse event rates between the treatment groups based on age. No adverse event was reported for more than 1 subject within each age group, with the exception of headache, which was reported for two 5-year-old placebo subjects and two 11-year-old placebo subjects. There were no apparent trends in adverse event rates between the treatment groups based on sex and race, although the proportions of subjects in each subgroup were small.

Clinical Laboratory Evaluations

Mean changes from Baseline were examined for vital signs (diastolic and systolic blood pressure, heart rate, and respiration rate) after 1 and 2 weeks of treatment. No mean changes in vital signs indicative of a treatment effect were observed among subjects at either time point, regardless of age group or treatment. Results of vital signs evaluations stratified by age, race, and sex showed no meaningful differences between subgroups.

No clinically relevant changes in median laboratory test values were observed between treatment groups. Median percent changes in laboratory results, stratified by age, race, and sex showed no trend of a differential response in change from Baseline.

The majority of subjects of all age groups remained within the normal range at Endpoint and no clinically significant trends were observed. None of the individual changes was considered an adverse event and no subject was discontinued from the study because of a laboratory abnormality.

Clinically meaningful laboratory abnormalities were pre-defined by the sponsor as a blood chemistry value ≥ 2.6 times the upper limit of normal, haemoglobin concentration ≤ 9.4 g/dL, platelet count $\leq 74{,}000/\mu L$, or white blood cell count (WBC) $\leq 2{,}900/\mu L$. These definitions have been utilised by the sponsor in studies involving subjects with other allergic conditions. The investigator also determined if these changes had clinical relevance.

Two subjects in the 2- to 5-year old group (desloratadine 1.25 mg, 2) had values that met at least 1 of these criteria. One desloratadine subject had a low haemoglobin (9.5 g/dl) at Screening that was also low (9.3 g/dl) at the Final visit. A second desloratadine subject had a markedly elevated alkaline phosphatase (1186 U/l) at Screening that was repeated 1 day later and found to be within the reference range (243 U/l); at the Final visit, it was slightly above the reference range (398 U/l). No follow-up data were available. All values were judged by the investigator to be of no clinical relevance.

Three subjects in the 6- to 11-year old group (desloratadine 2.5 mg, 1; placebo, 2) had values that met at least 1 of these criteria. One placebo subject had liver function tests (ALT/AST) in the normal range at Screening and had elevated levels at the Final visit (338 U/l, 214 U/l, respectively). The elevations were not considered clinically significant and the subject was asymptomatic at study completion. No follow-up data were available. The other 2 subjects (1 desloratadine, 1 placebo) had abnormal laboratory test values (platelet count, creatinine, respectively) at Screening that normalised at the Final visit. The single abnormal value at final visit, when taken in the overall context of the experience with loratadine in children and adults, and the desloratadine clinical program in adults, is not considered clinically relevant.

Cardiovascular Safety

Data from the recently approved application for desloratadine 5.0 mg tablets demonstrated no indication of any cardiovascular concerns for desloratadine. No clinically relevant effect of desloratadine on any electrocardiographic parameter was observed in clinical pharmacology studies conducted at 9 times the proposed clinical dose of 5.0 mg, or in combination with drugs that have the potential to interfere with its metabolism.

Of the 231 subjects in the desloratadine syrup clinical program, no treatment-emergent adverse events categorised as general cardiovascular or heart rate and rhythm disorders were reported; there were no noteworthy differences among age, race, and sex subgroups. Vital signs evaluations showed that there were no meaningful differences in heart rate associated with desloratadine syrup compared with the placebo treatment. Overall, the majority of ECGs were normal at both Baseline and at Endpoint. There

were no apparent differences among any of the treatment groups in ECG intervals, and no noteworthy differences among age, race, and sex subgroups. Statistically significant differences in ventricular rate were observed in desloratadine syrup-treated subjects compared to placebo, but were not considered clinically relevant.

ECGs were recorded at Baseline (last measurement occurring on or before treatment start date) and within 1 to 3 hours after dosing following 1 week of treatment and also following 2 weeks of treatment. In addition to the analyses of the measured intervals QT, PR, and QRS, and the ventricular rate (VR), analyses of the calculated parameters, Fridericia QTc and Bazett QTc, were also performed.

Changes from Baseline were categorised according to the following definitions: less than 30 milliseconds, 31 to 60 milliseconds, or 61 or more milliseconds.

The majority of ECGs, regardless of age or treatment group, was within normal limits at Baseline and remained so after 1 and 2 weeks of treatment. No differences between treatments were apparent. Abnormal ECG results are shown in the table below.

Abnormal ECG Results

		Screening		Final Visit	
Subject Sex	Parameter	Day 1 Visit 1	Day 8 Visit 3	Day 15 Visit 4	Comment
DL 1.25 mg					
P00303-068 Male	Ventricular Rate (bpm)	170	102	119	Sinus tachycardia Not clinically significant Left axis deviation QRS 31°
P00303-115 Female	Ventricular Rate (bpm)	167	160	122	Sinus tachycardia Not clinically significant
P00303-080 Male	Bazett QTc (msec)	388	452	451	Prolonged QTc (Visits 3,4)
	Fridericia QTc (msec)	368	411	418	Not clinically significant
	Ventricular Rate (bpm)	82	106	94	
DL 2.5 mg					
P00302-037 Male	Ventricular Rate (bpm)	65	63	59	Sinus bradycardia Not clinically significant
P00302-071 Male	Ventricular Rate (bpm)	59	66	54	Sinus bradycardia Not clinically significant
P00302-045 Female	Bazett QTc (msec)	477	399	405	Prolonged QTc (Visit 1)
	Fridericia QTc (msec)	436	387	371	Not clinically significant
Placebo					
P00303-061 Male	Ventricular Rate (bpm)	146	168	105	Sinus tachycardia
	Bazett QTc (msec)	452	415	397	Not clinically significant
	Fridericia QTc (msec)	390	350	362	Prolonged QTc (Visit 1)
P00302-038 Male	Ventricular Rate (bpm)	65	62	54	Sinus bradycardia Not clinically significant
P00302-077 Male	Bazett QTc (msec)	409	398	473	Prolonged QTc (Visit 4)
	Fridericia QTc (msec)	381	365	422	Not clinically significant
P00302-105 Male	Bazett QTc (msec)	444	428	453	Prolonged QTc (Visit 4)
	Fridericia QTc (msec)	426	417	431	Not clinically significant
P00302-086 Female	Left ventricular hypertrophy	Yes	Yes	Yes	Left ventricular hypertrophy Not clinically significant. (Further evaluation: ectopic atrial rhythm with high voltage)
P00303-090 Female	Bazett QTc (msec)	471	453	426	Prolonged QTc (Visit 1)
	Fridericia QTc (msec)	422	413	390	Not clinically significant
P00303-117 Male	Bazett QTc (msec)	468	429	441	Prolonged QTc (Visit 1)
	Fridericia QTc (msec)	414	394	401	Not clinically significant

Among the 2- to 5-year olds, 2 subjects in the desloratadine 1.25 mg group had abnormal ECGs (sinus tachycardia 170 bpm and left axis deviation QRS 31°; sinus tachycardia 167 bpm) at Baseline that normalised by Day 15. One subject in the placebo group had a normal ECG at Baseline (146 bpm) that was abnormal (168 bpm, sinus tachycardia) at Day 8, but normalised by Day 15 (105 bpm).

Due to the higher heart rates in children and due to the "over correction" of the Bazett formula at higher heart rates, there were substantial differences between the QTc-values corrected by the Fridericia and the Bazett formula. One male subject in the desloratadine 1.25 mg group had an increase of the Bazett QTc by a maximum of 63 msec and of the Fridericia QTc by a maximum of 50 msec. Another subject in the placebo group had an increase of the Bazett QTc by a maximum of 64 msec and of the Fridericia QTc by a maximum of 41 msec. Other subjects had major shortenings over Baseline. The pattern observed was a random pattern without evidence for a drug effect.

Among the 6- to 11-year olds, 3 subjects (desloratadine 2.5 mg, 1; placebo, 2) had normal ECGs at Baseline that were abnormal at Day 8 or Day 15, and 1 subject (DL 2.5 mg) had an abnormal ECG at Baseline that was normal at Day 8 and abnormal at Day 15. None of the changes were considered clinically significant. The abnormal ECG findings included sinus bradycardia (DL, 2; placebo, 1) and left ventricular hypertrophy (placebo). A further review of serial ECGs by the sponsor of the left ventricular hypertrophy ECG showed an ectopic atrial rhythm with high voltage, not clinically significant, and not suggestive of left ventricular hypertrophy. This remained unchanged from Baseline throughout the treatment.

There were no statistically significant differences between the treatment groups in the ventricular rate, PR, QRS, QT, Bazett QTc or Fridericia QTc intervals at Baseline in either age group.

Statistically significant differences between the two treatment groups in the 2- to 5-year old group were noted for change from Baseline in ventricular rate (Day 8 and Day 15; $p \leq 0.039$) and QT interval (Day 15; $p = 0.046$), but the differences were not considered clinically meaningful. Mean values for ventricular rate in the desloratadine treatment group (102.1 bpm at Baseline) showed a temporary increase at Day 8 (+4.29), then normalised at Day 15 (-0.71). Mean QT interval values for the desloratadine treatment group (Baseline 319.6 msec) showed an increase of 3.56 by Day 15, while for the placebo group (Baseline 318.3 msec) there was an increase of 13.04. There was no statistically significant difference between treatments in the change from Baseline for PR, QRS, Bazett QTc or Fridericia QTc intervals at either post baseline time point. No subject had a Fridericia QTc greater than 430 msec at either time point.

There were no statistically significant differences between treatment groups in the 6- to 11-year old group for change from Baseline in ventricular rate, PR, QRS, QT, or Fridericia QTc intervals at either post baseline visit. One male subject in the placebo treatment group with a Baseline QTc of 419 msec had a Fridericia QTc interval of 445 msec (slightly above the normal reference range) after 2 weeks of treatment. No apparent trends for mean change and mean percent change from Baseline in ECG values were observed by age, sex, and race.

For all ECG intervals, the percent change from Baseline for the majority of subjects was between -10% and < +10% at both post baseline visits. There were no apparent differences between desloratadine 1.25 mg, desloratadine 2.5 mg, and placebo for any of the ECG intervals. Subjects in the desloratadine groups had a greater frequency of increases ≥ 20% in ventricular rate compared with the respective placebo groups. Among subjects in the 2- to 5-year old group, 8 (15%) desloratadine subjects and 2 (4%) placebo subjects had increases ≥ 20% at both Day 8 and Day 15. Among subjects in the 6- to 11-year-old group, 4 (7%) desloratadine subjects and 1 (2%) placebo subject had increases ≥ 20% at Day 8, and 3 (5%) desloratadine subjects and 2 (3%) placebo subjects had increases ≥ 20% at Day 15. None of these changes were considered clinically significant.

Hepatic and Renal Safety

Safety data from the 2 Phase-III paediatric studies for desloratadine syrup uncovered no particular safety concerns relevant to the hepatic or renal system. Of the 231 subjects in the desloratadine syrup clinical program, no subject from the desloratadine group experienced adverse events associated with the hepatic or renal system.

Post-marketing surveillance

Based on the assessment of the first PSUR the MAH concluded that during the exposure period of January to June 2001, 26 spontaneous reports with allergic drug reactions were received. The reporting rate was 0.002% (26/1,300,000). The ADRs include a number of specific and non-specific

descriptions of reactions, such as pruritus, rash, urticaria, angioedema and bronchospasm. The following sentence was added to section 4.8 of the SPC and section 4 of the PL through a Type II variation:
"Very rare cases of hypersensitivity reactions, including anaphylaxis and rash, have been reported during the marketing of desloratadine".

The following terms were introduced in section 4.8 of the SPC and section 4 of the Package Leaflet through a Type II variation following the assessment of the third PSUR: “elevated liver enzymes”, “bilirubin increased”, “tachycardia”, “palpitations”, “diarrhoea”, “dyspepsia”, “abdominal pain”, “nausea” and “vomiting”. The statement regarding hypersensitivity was modified to mention the terms “angioedema”, “pruritus” and “urticaria”. These events were reported very rarely during the post-marketing period. Furthermore, section 4.8 of the SPC was reorganised by system organ class as requested by the CPMP.

Following the assessment of the fourth PSUR the following terms: ‘somnolence’ and ‘dizziness’ were included in the SPC. The addition of the term ‘somnolence’ was reflected in subsequent changes to section 4.7 (Effects on ability to drive and use machines) and 5.1 (Pharmacodynamic properties) of the SPC. These changes were also reflected in the Package Leaflet.

Desloratadine and hypospadia

On 25 April 2002, Sweden triggered a referral to the EMEA under Article 31 of Directive 2001/83/EC for loratadine containing medicinal products. The reason was data from the Swedish Medical Birth Registry (SMBR) suggesting that the use of loratadine during the first trimester of pregnancy may be associated with increased risk of hypospadias (a non-life threatening condition in which the opening of the penis is on the underside rather than the tip of the penis). As desloratadine is the major metabolite of loratadine a referral was therefore also triggered for desloratadine containing medicinal products. The separate referral procedure for loratadine containing medicinal products is not addressed in this EPAR since the CPMP is also assessing other aspects of the safety and efficacy of these nationally approved products. The following scientific discussion therefore only refers to the scientific discussion and conclusions for the desloratadine referral.

Studies Conducted to Date

Swedish Medical Birth Registry (SMBR)
In Sweden, drug use is recorded at the first antenatal care visit, which for at least 90% of pregnant women is made before week 14 of pregnancy. The recorded drug use in the first trimester is entered into the SMBR, and these data are thereafter linked to data on pregnancy outcome. Thus, drug use is recorded prospectively to pregnancy outcome. Nearly all deliveries (at least 98%) in Sweden are reported to the SMBR, i.e. about 90 000 / year, and the database contains more than 500 000 pregnancies.

In an analysis of data from the SMBR in November 2001, 15 cases of hypospadias were identified among 2,780 loratadine-exposed pregnancies. The total prevalence of hypospadias observed in the SMBR is 2.1 out of 1000 pregnancies (boys and girls). The corresponding figure in children (boys and girls) born by mothers who claim to have taken loratadine during early pregnancy was 5.4. The overall adjusted odds ratio, stratifying for year of birth, maternal age and parity, was 2.3 [95% CI 1.4-3.6]. Among the 15 cases, the severity was recorded as mild in 11 cases, moderate in one case and not recorded in 3 cases.

Hypospadias is a relatively common malformation. Reported background incidences show large variation; however, the CPMP found that the total prevalence of hypospadias in the SMBR falls within the reported background incidences of 0.5 to 3 per 1000 live births.

The CPMP considered that possible biases that have been identified in the SMBR, including misclassifications, would bias the risk estimate towards 1 or not affect it. The existence of misclassifications should be viewed as contributing to the strength of the signal. That the effect of non-differential misclassification bias is to underestimate the real association is in line with known

epidemiological theory and experience. That there would be any bias in the opposite direction e.g. through the recording of the drug use (the outcome of the pregnancy is not known at the time of the antenatal visit) or the diagnosis of hypospadias is unlikely. The CPMP found that the known confounding factors have been corrected for in the analyses (e.g. parity, smoking, age etc).

The SMBR has analysed the occurrence of hypospadias with other antihistamines used for allergy treatment. The CPMP concluded that there is no indication of a class effect, of a relation to underlying disease or a bias against this group of products as a whole.

Outcome of pregnancies in women taking desloratadine or loratadine

As of June 1 2002, the MAH's post-marketing surveillance database contained 4 cases involving a pregnancy and maternal exposure to desloratadine. No cases of foetal disorder or birth defects, including hypospadia, were reported.

The MAH had received approximately 250 reports of loratadine use during pregnancy. These included the 15 hypospadia cases from the SMBR, and 8 spontaneous reports that were received following the initiation of the Article 31 referral procedure. Based on these reports and taking the estimated worldwide use of loratadine (over 15 10^9 patient days of therapy) into account, the CPMP concluded that the spontaneous reporting data did not raise concerns regarding the use of loratadine during pregnancy. On the other hand, considering an expected considerable underreporting, these data are not robust enough to conclude that use of loratadine during pregnancy is safe.

No reports of hypospadias associated with loratadine/desloratadine were identified in a search of the published literature. Three studies comparing the outcomes of loratadine-exposed pregnancies to controls were identified.

The CPMP concluded that the three published studies do not indicate an increased risk of congenital malformations with loratadine/desloratadine use. However, the total number of women exposed to loratadine in these studies is less than 200, which is too low to conclude on the lack of risk.

Preclinical studies

External Male Genitalia Development and Importance of Androgens

The CPMP concluded that antiandrogenic activity is the only currently known non-genetic mechanism for induction of hypospadias. Nevertheless, there are examples where an association between hypospadias and drug intake have been demonstrated in humans e.g. insulins and valproic acid. In these cases, possible mechanisms have not been established, but they are probably not directly related to antiandrogenic activity.

Moreover, the CPMP considered that there is no evidence from the literature or other sources supporting that hypospadias induced via the known mechanism may occur without signs of other hormonally related effects i.e. signs of antiandrogenic actions.

Antiandrogenic endpoints in loratadine /desloratadine studies

The CPMP assessed a number of parameters addressing antiandrogenic potential, including hypospadias in the loratadine and desloratadine reproductive toxicity studies. One of these studies was designed specifically to evaluate the potential antiandrogenic effect of loratadine in male rat offspring. The CPMP considered that the results of this study demonstrated that loratadine did not affect the development of the male F_1 genital tract, including hypospadias, in rats exposed throughout organogenesis and early postnatal development (up to day 4 post partum). The CPMP concluded that there was no indication of antiandrogenic effects in the studied endpoints.

Other birth registries and Case Control Studies

The MAH presented results from two other birth registries. When combined they provide experience in 318 loratadine-exposed women during the first trimester of pregnancy. Examination revealed no reports of hypospadias associated with maternal loratadine use and no evidence of an increased rate of major congenital abnormalities among offspring of mothers exposed to loratadine during the first trimester.

The CPMP considered that the presented registry data tend to confirm that loratadine/desloratadine does not represent a major teratogenic risk. However, even if no association between loratadine/desloratadine and hypospadia was identified, it can not be concluded that loratadine/desloratadine does not increase the rate of hypospadias since the number of pregnancies in the registries was too small.

The MAH provided preliminary results from a case control study. The CPMP concluded that the preliminary results show no increase in the odds ratio compared to a standard control population. However, the sample size was limited and the confidence interval wide.

Overall conclusion on desloratadine and hypospadia

The CPMP concluded that the safety findings regarding hypospadia emerging for loratadine are considered to be relevant also for desloratadine, being the major metabolite of loratadine, until the opposite has been demonstrated.

The CPMP concluded that the benefit/risk balance of desloratadine remains favourable and that the available preclinical data for desloratadine/loratadine does not indicate that desloratadine has either genotoxic or antiandrogenic potential.

The CPMP concluded that the SMBR provides a robust signal that loratadine exposure during pregnancy increases the risk of hypospadia. Reasonable biases that have been identified in the SMBR, including misclassifications, cannot explain the occurrence of the signal. Hence, the current finding is either a chance finding or a true drug effect. The preclinical data argue against a true drug effect. Thus, based on the available data, a causal relationship can neither be confirmed nor excluded. As a precautionary measure the CPMP recommended, that the SPC for desloratadine containing medicinal products should be amended to state that the use of desloratadine during pregnancy is not recommended. This change to section 4.6 of the SPC and section 2 of the Package Leaflet was introduced through a Type II variation.

The CPMP concluded that continued monitoring of desloratadine is warranted and that the signal should be further investigated.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of the film-coated tablets is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

The quality of the oral lyophilisate and the syrup is considered to be acceptable when used in accordance with the conditions defined in the SPC. Satisfactory evidence is provided that product manufacture is well controlled, that consistency of manufacture is achieved and that stable products results.

Preclinical pharmacology and toxicology

Desloratadine is the major active metabolite of loratadine. It is a more potent H_1 receptor antagonist than loratadine itself and in most preclinical studies desloratadine C_{max} and AUC were higher after desloratadine than after an equimolar dose of loratadine. In particular, desloratadine is also a more potent antimuscarinic agent than loratadine when tested at concentrations and doses which far exceed those which exhibit antihistamine activity. Furthermore, this activity of desloratadine is not considered to be of clinical relevance.

The genotoxicity studies showed that neither desloratadine nor the major human metabolite 3-hydroxy-desloratadine are genotoxic.

The isoenzyme responsible for the major human metabolic pathway of desloratadine, e.g. hydroxylation in position 3 remains to be identified. However, polymorphism seems not to be related to the classical CYP isoenzymes. Therefore, the drug interactions are anticipated to be less than for loratadine.

Taking into account that the desloratadine conventional 5-mg tablet formulation and the desloratadine syrup and oral lyophilisates are bioequivalent, and based upon the pre-clinical data presented for the film-coated tablet, no toxicological concerns were raised regarding the use of the desloratadine syrup or oral lyophilisate formulations.

Efficacy

Film-coated tablet

The data provided support the claim that doses of 5 mg or 7.5 mg are effective in reducing symptoms of Seasonal Allergic Rhinitis as compared to placebo. The results are corroborated by a pooled analysis of the four trials, which showed desloratadine 5 and 7.5 mg to be superior to placebo and the effect of the two desloratadine doses not to be significantly different.

However, although the mean change following desloratadine 5 and 7.5 mg might be statistically significantly higher than following placebo, the numerical difference is small. The reduction of symptom scores was between 25 and 30% from baseline, which seems to be in concordance with the effect seen for other antihistamines in SAR. However, it seems from the percentage of improvement in Total Symptom Score that the clinical efficacy of 5 mg desloratadine is probably not superior to 10 mg loratadine.

The efficacy of desloratadine has not been studied in active comparator trials. This was found to be acceptable, as desloratadine is the active metabolite of loratadine, which has been on the market for a long time. Moreover, pharmacokinetic data show that desloratadine exposure is essentially similar after 5 mg desloratadine and 10 mg loratadine.

The symptom cough was evaluated in 3 out of 4 studies (C98-223, C98224 and C98-225). In none of these studies did the mean change between baseline and post treatment values attain statistical significance compared to placebo. This is also the case for the symptom nasal congestion.

The onset of action for desloratadine has been demonstrated to occur from 1 to 2 hours after administration.

Data provided in a Type II variation was found to support the extension of the indication to Allergic Rhinitis. The data showed that 5 mg desloratadine was effective in reducing the symptoms of AR compared to placebo.

Data provided in a Type II variation was found to support the extension of the indication to include Chronic Idiopathic Urticaria. The data showed that 5 mg desloratadine was effective in reducing the symptoms of CIU compared to placebo.

Oral lyophilisate

The DL 5 mg film-coated tablet has been found to be effective in the treatment of allergic rhinitis and chronic idiopathic urticaria. Bioequivalence of plasma profiles of the DL 5 mg oral lyophilisate and DL 5 mg film-coated tablet supports the efficacy of the DL 5 mg oral lyophilisate formulation.

Syrup

The Clinical Pharmacology program completed by the sponsor has adequately evaluated the pharmacokinetics of desloratadine syrup in paediatrics.

The exposure of desloratadine in 2- to 5- and 6- to 11-year olds, following the administration of a single 1.25 mg and 2.5 mg dose of desloratadine syrup, respectively, is comparable to the exposure observed in adults following a single dose of desloratadine 5.0 mg tablet.

Based on the demonstrated safety and efficacy of desloratadine in adults, and also on a favourable safety and efficacy profile from the considerable loratadine syrup exposure in the paediatric population, it is anticipated that desloratadine syrup will be safe and efficacious in the paediatric population.

The bioavailability of the syrup formulation is unaffected by the concomitant administration of food.

It is considered acceptable to extrapolate paediatric efficacy of desloratadine from the desloratadine efficacy studies in adults, as a full clinical program has been performed with desloratadine in adults

and since the nature and course of the diseases (allergic rhinitis and CIU) are similar in adults and paediatric patients.

Safety

Film-coated tablet

In a pooled analysis of safety data from ten studies of DL 5mg tablet in several indications (including the AR and CIU indications) the most common related TEAE was headache with 4.5% in subjects in the desloratadine 5 mg group and 3.9% in the placebo group. Other frequently reported TEAEs were dry mouth (2.6% for desloratadine, 1.8% for placebo), fatigue (1.8% for desloratadine, 0.6% for placebo) and somnolence (1.9% for both desloratadine and placebo).

Most of the AEs reported during the studies were graded as mild to moderate in severity. The overall incidence of severe adverse events in the SAR studies was similar among the treatment groups with 3-5% in the desloratadine groups and 3% in the placebo group. In the CIU studies severe treatment related adverse events occurred in less than 1% in both treatment groups.

Neither the mean values QTc nor the individual changes showed an effect of desloratadine on QTc compared to placebo.

The polymorphism in the metabolism of desloratadine did not lead to higher adverse event rates or new adverse events and it was not associated with a change in cardiovascular safety.

The enzyme(s) as well as the tissue site(s) responsible for the metabolism of desloratadine to its primary metabolite 3-OH-desloratadine has not yet been identified. However, it is anticipated that the potential for PK interactions of desloratadine is low, as the metabolism does not appear to be mediated by a known cytochrome P450 enzyme and the drug is neither a substrate or an inhibitor of p-glycoprotein.

Normal metabolisers with moderate hepatic impairment could experience a 3-fold increase in the desloratadine exposure (median AUC). However, no apparent difference between the exposure to desloratadine in slow metabolisers with and without hepatic impairment was seen. Given that the increase in median exposure between normal and poor metabolisers is 6-fold and that there is no major differences in the safety profile for poor and normal metabolisers a dose reduction is not recommended in patients with hepatic impairment.

Patients with varying degrees of renal impairment, who were normal metabolisers has a 1.5-2.5 fold increase in AUC for desloratadine and minimal changes in 3-OH-desloratadine concentrations, therefore a warning concerning the use in patients with renal impairment is recommended. This is reflected in the SPC (see section 4.4 Special warnings and special precautions for use).

Oral lyophilisate

The DL 5 mg film-coated tablet has been found to be safe in the treatment of allergic rhinitis and chronic idiopathic urticaria. Bioequivalence of plasma profiles of the DL 5 mg oral lyophilisate and DL 5 mg film-coated tablet supports the safety of the DL 5 mg oral lyophilisate formulation.

Syrup

Adverse events, vital signs, and ECG data from the Phase-III clinical trials in the syrup clinical program uncovered no significant indication of cardiovascular concerns with desloratadine syrup at the proposed dosages for children 2 to 11 years of age.

Benefit/risk assessment

Film-coated tablet

The overall benefit/risk assessment is considered to be positive considering that

- the clinical efficacy as compared to placebo seems comparable to other established antihistamines, although the efficacy of 5 mg desloratadine is probably not superior to 10 mg of loratadine

- although the isoenzyme responsible for the major human metabolic pathway of desloratadine remains to be identified, the polymorphism seems not to be related to the classical CYP isoenzymes and drug interactions are therefore anticipated to be less than for loratadine
- there are no safety issues including changes in cardiovascular safety associated with desloratadine or the observed polymorphism.

Oral lyophilisate

The overall benefit/risk assessment is considered to be positive considering that

- Desloratadine 5 mg film-coated tablet is considered a safe and effective dose in the treatment of AR and CIU in adults and adolescents.
- Pharmacokinetic studies have shown that oral administration of a 5 mg oral lyophilisate is bioequivalent to a dose of 5 mg desloratadine film-coated tablets

The DL 5 mg film-coated tablet has been found to be safe in the treatment of allergic rhinitis and chronic idiopathic urticaria. Bioequivalence of plasma profiles of the DL 5 mg oral lyophilisate and DL 5 mg film-coated tablet supports the safety of the DL 5 mg oral lyophilisate formulation.

Syrup

The overall benefit/risk assessment is considered to be positive considering that

- Desloratadine 5 mg film-coated tablet is considered a safe and effective dose in the treatment of AR and CIU in adults and adolescents.
- Pharmacokinetic studies have shown that oral administration of a 5 mg desloratadine syrup is bioequivalent to a dose of 5 mg desloratadine film-coated tablet in adults

The exposure of desloratadine in 2- to 5- and 6- to 11-year olds, following the administration of a single 1.25 mg and 2.5 mg dose of desloratadine syrup, respectively, is comparable to the exposure observed in adults following a single dose of desloratadine 5.0 mg tablet.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Aerius in relieving the symptoms of allergic rhinitis and of chronic idiopathic urticaria was favourable and therefore recommended the granting of the marketing authorisation for Aerius 5 mg film-coated tablet, Aerius 5 mg oral lyophilisate and Aerius 0.5 mg/ml syrup.