SCIENTIFIC DISCUSSION

1 Introduction

Seasonal allergic rhinitis (SAR) is the most commonly reported allergic disease, affecting an estimated 23% of the population in Europe. The characteristic symptoms of SAR include sneezing, rhinorrhea, nasal pruritus, eye symptoms, palatal itching and congestion. Antihistamines are recommended for use as first-line therapy in SAR. However, antihistamines may not provide adequate relief to patients with nasal congestion. This justifies the need for combining an antihistamine with a nasal decongestant. First-generation antihistamines have been shown to cause significant adverse events (AEs), particularly sedation. By comparison, second-generation antihistamines, such as desloratadine (DL) lack appreciable CNS effects and have a greater affinity for H_1 receptors, with a slower dissociation rate and a longer duration of action. This is the application for the desloratadine/pseudoephedrine sulphate (DL/PSE) prolonged release tablet in the symptomatic treatment of SAR when accompanied by nasal congestion in patients 12 years and over. The DL D-12 tablet (2.5 mg DL/120 mg PSE) comprises two layers, an immediate release layer of 2.5 mg DL and a sustained release layer of 120 mg PSE, designed for twice-daily dosing. DL, an active metabolite of loratadine (L), is a long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic activity that possesses peripheral antihistaminic effects. The MAH claimed that DL has no sedative or other central nervous system effects at clinically recommended doses. DL is currently approved in over 95 countries in the symptomatic treatment of allergic rhinitis and chronic idiopathic disorders (CIU). PSE is a widely used over-the-counter oral nasal decongestant. Several different combinations of anti-histamine drugs in fixed combination with pseudo-ephedrine have been registered in Europe. In 2001 a marketing authorisation was granted via the centralised procedure for DL 5 mg tablet In November 2003 a referral on L containing products (including the MRP product containing fixed combination of L plus PSE]) has been closed, giving confirmation that those products have a positive risk-benefit in this indication. At effective recommended oral dosages, PSE minimally produces other sympathomimetic effects, such as pressor activity and central nervous system stimulation. An antihistamine alone may not provide adequate relief to patients with nasal congestion, which justifies the need to combine an antihistamine with a nasal decongestant. The data presented in this submission demonstrate that the DL D-12 combination tablet is safe and more effective than either component alone in relieving the symptoms of SAR, including nasal congestion. Currently, the DL D-12 tablet is available only in the USA, and plans are under way to seek approval in other countries as well. Another combined product, DL 5 mg and PSE 240 mg, designed for once-daily administration, is also available in the USA. The clinical program conducted to support the DL D-12 tablet application comprised two Phase-3 active-controlled studies, which established efficacy and safety of the DL D-12 product.. To bridge the safety and efficacy data of the Phase-3 formulation (original) to the final formulation , a pivotal bioequivalence study was conducted with the two formulations. Three Phase-1 studies were conducted with the final formulation of the DL D-12 tablet to characterize its biopharmaceutical properties and establish an in vitro/in vivo correlation. The requested indication of DL D-12 is the symptomatic treatment of SAR when accompanied by nasal congestion in patients 12 years and over.

2 Quality aspects

Composition

Aerinaze is presented as an oval bilayer uncoated tablet. The blue immediate release layer contains 2.5 mg of desloratadine as the active substance and the white sustained release layer contains 120 mg of pseudoephedrine sulphate as the active substance.

Other ingredients of the immediate release layer are: maize starch, microcrystalline cellulose, edetate disodium, citric acid anhydrous, stearic acid, indigo carmine (E132), and aluminium lake.,

Other ingredients of the sustained release layer are: hypromellose 2208, microcrystalline, cellulose, povidone and magnesium stearate.

All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.

The tablets are packaged in clear blisters sealed with aluminium foil.

Active Substance

I. Desloratadine

The current dossier includes the scientific data on desloratadine that were submitted and approved for the desloratadine 5-mg film coated tablets.

The chemical name of desloratadine is 8-chloro-6, 11-dihydro-11-(4-piperidinylidene)-5H-benzo-[5,6]cyclohepta[1,2,-b]pyridine. Evidence of the chemical structure of desloratadine is confirmed by spectra from spectroscopic data.

It is a white to off-white powder, freely soluble in a number of organic solvents and very slightly soluble in water. Desloratadine has no chiral centre, but can exist in two polymorphic forms. The presence of polymorphs has no clinical relevance, since both forms exhibit very similar physicochemical properties and stability profiles, have similar dissolution profiles and are bioequivalent.

- **Manufacture**

Desloratadine is manufactured from loratadine in a synthetic process that uses commercially available materials.

All potential synthesis related impurities and degradation products have been adequately discussed in the dossier. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

- **Specification**

The specifications and test methods are those that have been previously approved in the centralised procedure.

The active substance specification includes tests for appearance, particle size (sizing instrumentation), identification (Ph. Eur.), assay (HPLC), related impurities (HPLC), polymorph content (spectroscopic), residual solvents (GC), moisture (Karl-Fischer) and heavy metals (Ph. Eur). Batch analysis data have been presented for batches used in preclinical safety, clinical and stability studies. In all cases the results were within the proposed specifications.

- **Stability**

Stability data have been presented for samples were stored for 36 months at 4°C/60%RH, 25°C/60%RH and 30°C/70%RH and for 6 months at 40°C/75%RH. Samples were also investigated under ICH light stress conditions.

In addition, results are presented for commercial scale batches, which were stored for 24 months at 25°C/60%RH and for 6 months at 40°C/75%RH. All samples were packed in small containers of the same material as the one intended for storing the active substance.

In all cases the results were in compliance with the proposed specifications and justify the proposed retest period.

Pseudoephedrine sulphate

Pseudoephedrine sulphate is a well known active substance described in a USP monograph. The Ph.Eur. includes a monograph for pseudoephedrine hydrochloride that has also been used as a reference.

The chemical name of pseudoephedrine sulphate is (1S,2S)-(+)-2-Methylamino-1-phenyl-propanol-(1) sulphate. It is a white to almost white crystalline powder that is very soluble in water and also hygroscopic.

- **Manufacture**

Data concerning the manufacturing process, in process controls and analytical methods used in the synthesis of pseudoephedrine sulphate have been presented using the Active Substance Master File (ASMF) procedure.

All potential synthesis related impurities have been adequately discussed in the dossier. The levels of the impurities are supported by the results of batch analysis data and appropriate specifications have been set.

- **Specification**

The specification includes the requirements of the USP monograph on pseudoephedrine sulphate, as well as a number of additional in house requirements. Some of those in-house requirements are based on the Ph.Eur. monograph on pseudoephedrine hydrochloride.

The active substance specification includes tests for appearance, identification, (IR, suphate), assay, purity (melting range, specific rotation, solution in water), heavy metals, loss on drying, residue on ignition, related substances (HPLC, TLC) and residual solvents (GC).

Batch analysis data have been presented for batches manufactured at the proposed manufacturing site. In all cases the results of batch analysis data were within the proposed specifications.

- **Stability**

Stability data presented for several batches monitored at 30°C/70%RH. Most of the batches were also fully monitored for 6 months at 40°C/75%RH. Samples stored at the 25°C/60% RH optional study condition were monitored for loss on drying, only.

The batches were tested for compliance with the proposed specifications with the exception of tests for identification, heavy metals, sulphated ash, chloride and residual solvents. Due to the hygroscopic nature of the substance, a fast moisture uptake is observed leading to out-of- specification results for loss-on-drying. However, it was demonstrated that this is mainly due to a non-representative product/surface ratio for the stability samples. Moreover, it has no clinical relevance since it neither leads to a decrease in assay results nor to an increase in degradation products.
For all other parameters the results were in compliance with the proposed specifications and justify the proposed retest period

Medicinal Product

- **Pharmaceutical Development**

Formulation development

The objective of the formulation development studies was to develop a tablet suitable for twice daily dosing that would allow the immediate release of desloratadine and a sustained release of pseudoephedrine sulphate. Therefore it was chosen to develop a bilayer tablet. The compatibility of the ingredients used in the two layers has been demonstrated.

The tablets are packaged in PCTFE /PVC/ Alu blisters. .

Process development

Process characterisation studies were performed to demonstrate the robustness and reproducibility of the manufacturing process.

- **Manufacture of the Product**

The manufacturing process consists of the following steps: preparation of the immediate and the sustained release layers separately by a standard wet granulation process and then compression of the two layers into bilayer tablets.

All critical process parameters have been identified and controlled by appropriate in process controls. Data from production scale verification stability batches demonstrate that the process is reproducible and provides a Medicinal Product that complies with the in-process and finished product specifications.

- **Product Specification**

The specifications for the finished product includes tests for appearance, release rate of the active substances (HPLC, UV), identification of the active substances, sulphate and preservatives (HPLC, TLC), assay for the active substances and preservatives, degradation products, residual solvents, moisture content, content uniformity (Ph. Eur.), hardness, friability and microbial quality (Ph. Eur.), All tests included in the specifications have been satisfactorily described and validated.

Batch analysis data have been presented for batches manufactured at the proposed manufacturing site. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- **Stability of the Product**

Stability results have been provided for batches manufactured at the proposed site and packed in the proposed blisters. Samples were stored for 18 months at 5°C/ambient RH, 25°C/60%RH and 30°C/65%RH, and for 6 months at 40°C/75%RH. Tablets were also exposed to photostability studies in accordance with the ICH requirements.

The samples were tested according to the specifications using stability indicating methods. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Aerinaze is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted that support the granting of the marketing authorization. There are no major deviations from the EU and ICH requirements.

The active substances are well characterised and documented. The specifications and scientific data for desloratadine, the active ingredient in the immediate release layer, correspond to those previously approved in the centralised procedure. Pseudoephedrine sulphate on the other hand is a well known active substance described in the USP. The Ph.Eur. includes a monograph for pseudoephedrine hydrochloride that has also been used as a reference. The suitability of the specifications proposed for pseudoephedrine sulphate has been demonstrated. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented.

The manufacturing process of the finished product has been adequately described. Proper controls have been established to ensure the adhesion between the two layers of the tablet. Appropriate product specifications have been established. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3 Non-clinical aspects

Introduction

No non-clinical pharmacology/ pharmacokinetic/ toxicology studies were conducted with the DL/PSE 12 hour tablet formulation. This approach, in the opinion CHMP is acceptable and justified in the way described below. A summary of the nonclinical pharmacology/ pharmacokinetic/ toxicology studies conducted with DL was submitted as part of the MAA for the conventional 5 mg tablet formulation (Original MAA Desloratadine EMEA/H/C/310-314 Commission decision: 15-Jan-01). PSE has been used clinically for many years, both alone and in combination with various antihistamines. Based on results of both animal and human studies, PSE is considered to be one of the safest orally-administered nasal decongestants presently available. The safety and efficacy of PSE as an orally-active nasal decongestant are evidenced by its long and widespread use in medical practice worldwide. A summary of

the nonclinical studies conducted with L/PSE was submitted as part of the MAA for the combination of L and PSE. A draft 'Guideline on the non-clinical development of fixed combinations of medicinal products' has been prepared by the EMEA (CHMP/SWP/258498/2005). The rationale for a combination therapy and a fixed combination is often that pharmacological or pharmacokinetic interactions are leading to improved efficacy or safety profiles, compared with the single components. The main aim with the non-clinical studies to support the clinical development of a fixed combination is to characterise potential additive, synergistic, potentiation or antagonistic effects of the compounds when used together and to characterise the pharmacology, pharmacokinetics and toxicology of the combination under development. When the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95). This is in the opinion of the CHMP the case for the DL/PSE combination, since sufficiently documented human experience is available for the L/PSE combination. A comparison of the DL studies with the previously submitted L studies indicate that the DL and L nonclinical safety profiles are similar. This is expected since DL is an active metabolite of L. Additional non-clinical studies with DL were submitted with this application and assessed here because they were performed after the DL were granted MA.

Pharmacology

No preclinical pharmacology studies were conducted with the DL/PSE 12 hour tablet formulation.

- Primary pharmacodynamics

DL is a non-sedating, long-acting histamine antagonist with selective peripheral H_1-receptor antagonist activity. After oral administration, DL selectively blocks peripheral histamine H_1-receptors because the substance is excluded from entry to the central nervous system. PSE is a sympathomimetic agent with mostly α-mimetic activity in comparison with the β-activity. PSE provides a nasal decongestant effect after oral administration due to its vasoconstrictive action. It has an indirect sympathomimetic effect due primarily to the release of adrenergic mediators from the post-ganglionic nerve endings.

- Secondary pharmacodynamics

DL has demonstrated antiallergic properties from *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed. Oral administration of PSE at the recommended dose can cause other sympathomimetic effects, such as increased blood pressure, tachycardia or manifestations of central nervous system excitation.

- Safety pharmacology programme

Central nervous system

DL 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 100 mg/kg. The lack of activity on the central nervous system is likely due to a lack of penetration through the blood-brain barrier.

Cardiovascular system

Studies have been performed to evaluate the effect of DL 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 DL: 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 and increases in QT intervals with high concentrations of DL. At some targets, L was more potent than DL, but the opposite was true in other models. In 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 DL (up to 12 mg/kg) do not exert effects on gastric emptying, intestinal transit time, renal and respiratory function.

Pharmacokinetics

No new nonclinical pharmacokinetics studies on absorption were performed with the combination. A bridge to the nonclinical pharmacokinetic, metabolism, and toxicity data used to support development of the DL/PSE 12 hour tablets is provided by the results from the SD and MD pharmacokinetic studies of DL 5 mg tablet, DL/PSE QD, and DL/PSE BID in humans. Exposure (Cmax and AUC) to DL, 3-OH DL, and PSE after single-dose (SD) and multiple-dose (MD) administration of DL in combination with PSE (DL/PSE 12 hour tablet formulations), DL alone, or PSE alone to humans was determined. The SD studies established that DL and 3-OH DL were bioequivalent after administration of DL/PSE 12 hour tablet and DL as a bilayer tablet (2.5 mg) and after administration of the two DL/PSE 12 hour tablet formulations. In addition, PSE was bioequivalent following administration of the original DL/PSE 12 hour tablet and a 120 mg PSE tablet formulation and after administration of the two DL/PSE 12 hour tablet formulations. A MD study conducted with the original DL/PSE 12 hour tablet (BID administration) demonstrated that exposure to DL, 3-OH DL, and PSE reached steady-state within 14 days. In addition, exposure [AUC (0-24 hr)] to DL and 3-OH DL at steady-state was comparable to that reported following MD administration of a 5 mg tablet of DL. Likewise, exposure to PSE was not different than that reported following administration of DL/PSE QD and DL/PSE BID. A MD study with the to-be-marketed DL/PSE 12 hour tablet formulation indicated that exposure to DL, 3-OH DL, and PSE reached steady-state within 10 days and exposures to DL, 3-OH DL, and PSE were not different than those observed with the original DL/PSE 12 hour tablet. Although mean AUC values for DL and 3-OH DL appeared to be lower after administration of the to-be-marketed DL/PSE 12 hour tablet, these differences are due to interindividual variability and are not expected to be clinically significant. Human PK data demonstrate that following oral administrations of DL/PSE 2.5 mg/120 mg tablet twice daily for 14 days in normal healthy volunteers, steady-state conditions were reached on day 10 for DL, 3-hydroxy-desloratadine and PSE. For DL, mean Cmax and AUC_{0-12h} of approx. 1.7 ng/ml and 16 ng•hr/ml were observed, respectively. For PSE, mean Cmax and AUC_{0-12h} of 459 ng/mL and 4658 ng•hr/m were observed. In the opinion of CHMP no new non-clinical PK studies with the combination are needed

Toxicology

- Single dose toxicity

Single-dose studies with the combination DL/PSE formulation have not been conducted.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose studies with the combination DL/PSE formulation have not been conducted. Three-month studies with the combination of loratadine and PSE have been conducted in rats and monkeys and were submitted in the L/PSE MAA. A summary of the nonclinical toxicology studies conducted with DL was submitted as part of the MAA for the conventional 5 mg tablet formulation. Dose-range finding studies in mice with DL were conducted after the submission of the marketing application for the DL 5 mg/day tablet and therefore were not previously presented in the DL 5 mg tablet MAA. These studies have not been conducted with the DL/PSE formulation and the results of these studies do not change the safety profile of any of the DL products.

Table. Repeated dose toxicity studies with DL not previously submitted.

Species	**Duration of Treatment**	**Report No.**
mice	Three-Month (Diet) Dose-Range Finding Study of DL	(SN 97253)
C57BL/6Ntac mice	Four Week Oral (Gavage) Dose Range-Finding and TK Study of DL	(SN 99261)

Three-Month (Diet) Dose-Range Finding Study of DL in Mice (SN 97253)

DL was administered orally to 6-week-old mice at daily doses of 24, 48, 96 or 192 mg/kg for three months. Doses of 24 and 48 mg/kg were well tolerated by male and female mice. Test article-related mortality was observed in two males given 192 mg/kg. Contributory causes of death or moribundity could not be determined based on necropsy and histopathologic findings. Mortality was attributed to

DL based on clinical observations of abnormal stool, mild to moderate dehydration, a hunched appearance possibly associated with impaired gastrointestinal clearance, and/or clinical signs of moribundity (hypoactivity, tremors, urogenital staining, no feces and coolness to touch). Abnormal stool also was seen in all surviving mice in the 48, 96 and 192 mg/kg dose groups. This observation correlated with distention of the large intestine at necropsy in the 96 and 192 mg/kg dose groups and may reflect a prolonged transit time through the large intestine related to the anticholinergic activity of high doses of DL. Mean body weights (MBW) of 192 mg/kg-dosed males and females were moderately lower (23.74% and 15.00%, respectively) than control values at study termination due to a MBW loss (males) or a reduction in MBW gain (females) during the overall dosing period. MBW gain values also were mildly lower in males given 48 or 96 mg/kg. No test article-related ophthalmoscopic findings were observed. Females administered 96 or 192 mg/kg exhibited minimally lower hemoglobin concentration and hematocrit. Mice given 96 or 192 mg/kg had minimally lower mean corpuscular volume and/or mean corpuscular hemoglobin without concurrently lower mean corpuscular hemoglobin concentration. Serum glucose concentration was mildly to moderately lower at 192 mg/kg. Females administered 192 mg/kg also had minimally higher serum phosphorus concentration. Alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase activities were minimally to moderately higher at 96 and 192 mg/kg. Serum cholesterol concentration was minimally to mildly lower in one female administered 96 mg/kg and in most mice receiving 192 mg/kg. Additionally, the incidence of serum triglyceride concentrations that were below detectable limits was higher at 96 (females only) and 192 mg/kg. The results of liver biochemistry analyses indicated that administration of 24, 48, 96 and 192 mg/kg caused induction of CYP2B1/2 in males and females and of CYP1A2 in males only. Furthermore, inhibition of activity of CYP2B1/2 was seen in males and females primarily at the higher doses of 96 and 192 mg/kg. An increase in CYP4A protein was detected in males at 96 and 192 mg/kg. The primary DL-related histopathologic finding in the 48, 96 and 192 mg/kg dose groups was cellular vacuolation (both epithelial and mesenchymal cells in several organs) consistent with phospholipidosis. The incidence and severity of vacuolation were dose-related. Findings associated with vacuolation included cellular swelling, degeneration, necrosis, hypertrophy and hyperplasia, which were organ- and cell-specific. Necrosis was associated with vacuolation in the kidney, epididymides, heart, and skeletal muscle. Increased cellular debris in the epididymides of 192 mg/kg-dosed males may have been sloughed epididymal epithelial cells. Analysis of testicular spermatid and epididymal sperm counts in mice at 96 mg/kg revealed no DL-related effects. Dose-dependent centrilobular hepatocellular hypertrophy was present in males at 48 and 96 mg/kg and in both sexes at 192 mg/kg. This finding correlated with higher mean absolute and relative liver weights at 96 and 192 mg/kg. Histo-pathologic observations of uterine atrophy in the 192 mg/kg dose group correlated with necropsy findings of small uteri. In addition, mean absolute and relative uterus weights were lower at 96 and 192 mg/kg. Thymic lymphoid depletion correlated with lower mean absolute and relative thymus weights at 192 mg/kg. Based on clinical observations of abnormal stool, higher blood urea nitrogen concentrations, and histopathologic findings seen at 48 mg/kg, the no-effect dose was 24 mg/kg under the conditions of this study. Based on mortality and decreases in MBW of 15% or greater, a dose of 192 mg/kg exceeded the maximum tolerated dose.

Four Week Oral (Gavage) Dose Range-Finding and TK Study of DL in C57BL/6Ntac Mice (SN 99261)

The potential toxicity of DL was assessed in C57BL/6NTac mice administered single daily oral (gavage) doses of 24, 48, 96, and 192 mg/kg for up to one month. The results of this study indicate that a no-effect level (NEL) in C57BL/6NTac mice was unable to be determined based on the test article-related changes in MBW gain, and leukocyte and lymphocyte counts at all dose levels. All mice in the 192 mg/kg were sacrificed on Day 8 due to excessive mortality. Clinical observations included few faeces, hunched appearance, hypoactivity, squinted eyes, cold to touch, labored respiration, and rough hair coat. Males also exhibited decreases in MBW, accompanied by transient decreases in mean food consumption in the Day 1-8 interval. This dose clearly exceeds the MTD. Test article-related clinical observations in surviving animals included few feces, hunched appearance, and hypoactivity. In addition, a dose-related decrease in MBW gain was observed in males and females in all dose groups relative to controls at the conclusion of the study. Body weight changes did not always correlate with decreases in mean food consumption in the affected groups. Alterations in the clinical chemistry data that are likely effects from DL administration included higher alanine

aminotransferase (ALT) values in 96 mg/kg/day males at Week 5. Findings in the clinical pathology data from males and females in the 192 mg/kg group at Week 2 that are considered indirect effects of dosing included lower values for total leukocyte and lymphocyte counts in one male, erythrocyte count (RBC), hemoglobin (HGB), and hematocrit (HCT) values in the females, relative and absolute reticulocyte counts (%RETIC and A RETIC values), total protein, albumin, and albumin/globulin (A/G) ratio values, and higher glucose and chloride concentrations in males and females. Total leukocyte and lymphocyte counts were also lower in most 24 and 96 mg/kg males at Week 5 relative to concurrent control males. DL-related necropsy findings were restricted to small thymic size in a single male mouse in the 192 mg/kg dose group. The procedures used to collect blood samples for toxicokinetic analyses were not in full compliance with GLP Regulations. Therefore, these data cannot be used in support of this study. The lowest dose employed in the current study (24 mg/kg) exceeds ICH Guidelines for establishing a maximum tolerated dose (10% decrease in body weight gain). Therefore, a maximum dose less than 24 mg/kg is indicated if a future 6-month p53 carcinogenicity study were to be conducted. The rationale for using C57BL/6NTac mice in this study was related to the project of conducting a 6 months carcinogenicity study in p53-deficient mice. No NOAEL could be established in this study. The applicant did not elaborate on the great sensitivity of this mouse strain to DL. Due to lack of GLP compliance TK data are missing. However, in the scope of this application, the CHMP considered that this preliminary study is of minor importance.

- Carcinogenicity

Carcinogenicity studies with the combination DL/PSE formulation have not been conducted. A carcinogenicity study in mice of DL has been conducted after the submission of the marketing application for the DL 5 mg/day tablet and therefore was not previously presented in the DL 5 mg tablet MAA. This study has not been conducted with the DL/PSE formulation and the results of this study do not change the safety profile of any of the DL products.

<u>24-Month Oral (Diet) Carcinogenicity Study of DL in Mice (SN 97255)</u>

The carcinogenic potential of DL was assessed in male and female mice administered single daily oral doses by dietary admixture. Males received doses of 4 or 16 mg/kg for at least 101 weeks or 48 mg/kg for at least 56 weeks. Females received doses of 10 or 32 mg/kg for at least 101 weeks or 96 mg/kg for at least 61 weeks. Because of excessive mortality dosing was stopped for high-dose males and females (48 and 96 mg/kg dose groups, respectively) but surviving mice continued on study (on control feed) after the cessation of drug administration and were sacrificed during Week 100. Mice in the remaining groups (0, 4, 10, 16 and 32 mg/kg) were sacrificed during Week 101/102. Additional mice in each DL-dosed group were evaluated only for plasma exposure during Weeks 4 and 24. Mice were systemically exposed to DL following dietary administration. Plasma DL conc. increased in a dose-related fashion. 3-hydroxy DL concentrations were not quantifiable. No increase in tumors was seen in any DL-dosed group compared to controls. Mortality associated with impaction, distention, dilatation and/or altered content of the large intestine was observed in males administered 16 or 48 mg/kg and in females dosed with 32 or 96 mg/kg. At the highest dose for each sex, a stress-related splenic lymphoid atrophy was associated with the intestinal findings. Increased mortality relative to controls was seen in male mice dosed with 16 or 48 mg/kg and in female mice dosed with 96 mg/kg DL. The increase in mortality was not related to carcinogenicity but to the pharmacologic (anticholinergic) effects of high doses of the drug. The MTD was exceeded at the highest dose for each sex based on the dose-limiting, pharmacologically mediated mortality observed. Clinical observations indicative of an anticholinergic effect on the GI tract were seen in a dose-related manner in all test article-dosed groups but occurred earlier in males administered 48 mg/kg and in females dosed with 96 mg/kg. MBW gain of 48 mg/kg-dosed males was 14% and 9% lower than for controls after six months and one year, respectively. This was associated with the poor condition and early sacrifice of many males in this dose group. After dosing with DL was terminated, body weights of the 48 mg/kg-dosed males showed recovery. MBW gain of females in all DL dose groups was greater than for controls at six months, one year and termination of dosing and may have been related to the anticholinergic effects of abdominal distension with retention of feces. Food consumption for males administered 48 mg/kg and females dosed with 96 mg/kg was lower during most intervals, even after dosing was terminated after approximately one year. In addition to the intestinal findings noted in decedents, distention of the large intestine was seen in two females in the 32 mg/kg dose group at terminal necropsy and correlated with histopathologic observations of luminal dilatation. The toxicity

observed in this study was related to the anticholinergic actions of DL, a known pharmacologic effect of histamine H_1 antagonists. Anticholinergic effects were also seen in previous studies of DL at high doses in mice, rats and monkeys[1, 2]. Anticholinergic effects are more common with first-generation H_1 antagonists but can also occur with second-generation H_1 antagonists at high doses. These effects were reversible as demonstrated by the decreased incidence of anticholinergic signs in 48 mg/kg-dosed males and 96 mg/kg-dosed females after cessation of drug treatment after approximately one year. No evidence of carcinogenicity was observed in this two-year dietary study in mice despite clear evidence that the MTD was exceeded in high-dose animals. No increase of tumor incidence was observed. In the opinion of the CHMP if the fixed combination contains compounds assessed as non-carcinogenic, carcinogenicity studies with the combination are not needed. In study SN 97255, because of excessive mortality, dosing was stopped after 56 or 61 weeks in the high dose group of both sexes. Mortality was associated with intestinal abnormalities (impaction, distension, dilation of large bowel). Body weight gain (BWG) was decreased in the male high dose groups, but increased in females in all dose groups. It was concluded that the decrease in BWG in males was due to increased mortality, while the increase in BWG in females may have been related to the anticholinergic effect of DL. However, both increased mortality and clinical observations of indicative of an anticholinergic effect on the GI tract are observed in both sexes. The applicant provided the explanation related to the observed sex differences in BWG. There appear to be definitive path of physiology to define the sex differences in BWG. However, taking into account the high safety margins: 85-fold, 321-fold and 1008-fold (mouse to human exposure multiples, female), and 493-fold (mouse to human exposure multiples, male), and the species (mouse) specificity of these findings, there is little risk to humans.

- Reproduction Toxicity

No new data were submitted with the combination. Teratology studies in rats and rabbits were conducted with combination of L and PSE and were submitted in the Loratadine/PSE MAA (Repetabs MAA submitted to Belgium HA approved Oct/04/1990 Registration number 304 S 117 F3). A summary of the nonclinical toxicology studies conducted with DL was submitted as part of the MAA for the conventional 5 mg tablet formulation (Original MAA DL EMEA/H/C/310-314 Commission decision: 15-Jan-01).

- Local tolerance

No data with the combination were submitted. DL/PSE is administered orally.

Ecotoxicity/environmental risk assessment

An ERA was conducted for DL according to the draft Guideline on the ERA of Medicinal Products for Human Use CPMP/SWP/4447/00, 20 January 2005. For DL, based on the calculations presented by the applicant, the PEN/PNEC ratios for water, soil, and sediment were less then one. Because of the low volatility, air was not expected route of environmental exposure. Therefore DL is not expected to have adverse events on environment. PSE is over-the-counter or generic medicinal ingredients within EU member countries. If a medicinal product has been on the marker for more then 8 years, no additional data are required beyond bioequivalence as per Directive 65/65/EC Article 10. There fore no further evaluation of PSE was provided with ERA. DL/PSE is thus considered unlikely to represent a risk for the environment following its prescribed usage in patients.

4 Clinical aspects

Introduction

DL is currently approved in over 95 countries in the symptomatic treatment of allergic rhinitis and chronic idiopathic disorders (CIU). PSE is a widely used over-the-counter oral nasal decongestant. An antihistamine alone may not provide adequate relief to patients with nasal congestion, which could justify the need to combine an antihistamine with a nasal decongestant. DL is extensively metabolized to 3-hydroxydesloratadine (3-OH DL), an active metabolite, which is subsequently glucuronidated. The enzyme(s) responsible for the formation of 3-OH DL have not been identified. Data from clinical

[1]SN97253 [S-31104] 3m (diet) dose-range finding study of DL in mice. Lafayette (NJ): Schering-Plough Res. Inst.; 2000.

[2]SN97016 [P-6973] 3m oral (gavage) toxicity study of DL in rats. Columbus (OH): Battelle; 1999.

trials with DL indicate that a subset of the general population has a decreased ability to form 3-OH DL, and are poor metabolizers of DL. No safety issues have been identified with DL in poor metabolizers. PSE is a widely used over-the-counter oral nasal decongestant. At effective recommended oral dosages, PSE minimally produces other sympathomimetic effects, such as pressor activity and CNS stimulation. Use of an orally administered vasoconstrictor for shrinkage of congested nasal mucosa has several advantages: a) It produces a gradual but sustained decongestant effect, causing little, if any, "rebound" congestion; b) it facilitates shrinkage of swollen mucosa in upper respiratory areas that are relatively inaccessible to topically applied sprays or drops; and c) it relieves nasal obstruction without the additional irritation that may result from local medication. Following single-dose oral administration of PSE as tablets or oral solution (30-mg or 60-mg doses), nasal decongestion occurs within 30 minutes and persists for 4 to 6 hours. Nasal decongestion may persist for 8 hours following oral administration of 60 mg of PSE and up to 12 hours following 120 mg of PSE in extended release formulations. PSE alone is incompletely metabolized (less than 1%) in the liver by N-demethylation to an inactive metabolite. The drug and its metabolite are excreted in the urine. About 55% to 96% of an administered dose of PSE is excreted unchanged in the urine.

The DL D-12 tablet is a bilayer tablet that provides immediate-release of 2.5 mg of DL) and sustained release of 120 mg of pseudoephedrine sulphate (PSE). This formulation is designed for twice-daily administration in subjects 12 years and over.

The clinical program conducted to support the DL D-12 tablet application comprised two Phase-3 active-controlled studies, which established efficacy and safety of the DL D-12 product., To bridge the safety and efficacy data of the Phase-3 formulation (original) to the to be marketed formulation, a pivotal bioequivalence study was conducted with the two formulations. Three Phase-1 studies were conducted with the final formulation of the DL D-12 tablet to characterize its biopharmaceutical properties and establish an in vitro/in vivo correlation.

Table. Summary of Studies Conducted With the two Formulations of DL D-12 Tablets

Protocol No.	Study Description	Study Design	Study Population
		Phase-3 Studies	
P00355	Efficacy and safety of DL+PSE, BID, versus its components in the treatment of subjects with SAR	Multiple dose Double blind Randomized Parallel group	598 patients with SAR Age 12-76 yr 224 M, 374 F
P00362	Efficacy and safety of DL+PSE, BID, versus its components in the treatment of subjects with SAR	Multiple dose Double blind Randomized Parallel group	650 patients with SAR Age 12-78 yr 221 M, 429 F

Protocol No.	Study Description	Study Design	Study Population
		Phase-1 Studies	
P02040	Bioequivalence of the original and new formulations of DL D-12	Single dose Open label Randomized 2-way crossover, replicate design	20 healthy subjects Age 23-45 yr 19M, 1F
P02041	Multiple-dose and steady-state pharmacokinetics of DL D-12	Multiple dose Open label	18 healthy volunteers Age 22 to 45 yr 9M, 9F
P02042	Food effect on the oral bioavailability of DL D-12	Single dose Open label Randomized 2-way crossover	20 healthy subjects Age 18-44 yr 10M, 10F
P02043	Bioavailability of PSE from controlled-release (12-hour) formulations	Single dose Open label Randomized 4-way crossover	20 healthy subjects Age 27-44 yr 10M, 10F

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Study P02040 (pivotal BE-Study):

The clinical program conducted to support the DL D-12 tablet application comprised two Phase-3 active-controlled studies, which established efficacy and safety of the DL D-12 product. The initial formula was used in these clinical trials to support the indications in this application. Subsequently, the formulation of the DL D-12 tablet was modified to improve on the stability of this product. To bridge the safety and efficacy data of the Phase-3 formulation to the improved formulation, a pivotal bioequivalence study was conducted with the two formulations.

Study-Design:
A total of 20 healthy subjects were enrolled and all 20 subjects completed this open label, randomized, two-sequence, four-period crossover study. The replicate cross-over design was recommended for the evaluation of bioequivalence of modified-release dosage forms. This design minimizes the residual variation due to subject differences and possible period effects, and allows comparison of within-subject variances for the test and reference products. A minimum of a ten-day washout was included to eliminate carry-over effects. Subjects were assigned to receive the following treatments twice in four separate periods: treatment A: DL D-12 tablet (Phase 3 formulation), treatment B: DL D-12 tablet (to be marketed formulation). Each subject was randomized to receive Treatment A and Treatment B in one of two sequences: ABAB or BABA. Blood samples were collected for the determination of pharmacokinetic parameters AUC (tf), AUC (I), Cmax, Tmax, and t (½) for DL, 3-OH DL, and PSE. The log-transformed AUC and Cmax values were statistically analyzed using a linear mixed effect model. The intrasubject variability for AUC and Cmax from DL D-12 in studies Study P00440 and Study P00446 was less than 16%. Assuming a larger intrasubject variability of 18%-24% for this single-dose, replicate crossover study it was estimated that with 20 subjects there should be at least an 80% chance of meeting the 80%-125% confidence interval with a 5% difference in formulations.

Data Sets Analyzed:
The safety population (n=20) included all subjects who were enrolled in the study and who received at least one dose of the study medication. The pharmacokinetic population (n=20) included all subjects who received treatment. However, only subjects with evaluable data in all treatment periods were included in the analysis of bioequivalence (n=16).

Pharmacokinetic Assessments for DL and 3-0H DL:
Subject Nos. 4, 5, 8, 9, and 19 had measurable predose DL concentrations. These predose DL concentrations were observed in the later phases of this study and thus, were most likely due to a carryover effect caused by an incomplete washout. In the second through fourth periods the predose DL concentration for Subject Nos. 4, 5, 9, and 19 represented 9-18% of Cmax values and according to the FDA guidance these subjects were dropped from bioequivalence evaluations for all three analytes. Inclusion of these subjects in bioequivalence evaluations did not change the conclusion of the study. Following oral administration, DL was gradually absorbed; mean Tmax was approximately 5 hours for both formulations. Mean exposure to DL (AUC [I]) was highly variable; mean AUC (I) CV.s ranged from 110 to 114%. DL was eliminated with a mean half-life (t½) of ~27 hours. The bioequivalence criteria were met for DL D-12 formulations. The 90% CI for DL Cmax and AUC (I) values (Treatment B/A) were 94.2-106% and 92.7-104% respectively. The within subject variability for log-transformed AUC (tf) and AUC (I) were larger for the old formulation (Treatment A) with ratios of the CV equal to 2.13 (=0.269/0.126) and 1.58 (=0.164/0.104), respectively. However, the variation was not large enough to impact the bioequivalence of each of the two treatments. Following oral administration, DL was extensively metabolized to 3-OH DL (an active metabolite). DL conversion to 3-OH DL exhibits a phenotypic polymorphism; approximately 7% of the population are classified as slow metabolizers of DL. A slow metabolizer of DL is defined as any subject with a 3-OH DL to DL AUC ratio of <10%, or has DL half-life >50 hours. Based on these criteria Subject Nos. 9 and 19 were identified as slow metabolizers. Subject No. 4 behaved like a slow metabolizer in 1 out of 4 periods (Treatment B, Period 3). This subject was not considered to be a slow metabolizer since his metabolite to parent exposure ratios were well above 10% in the other three treatment periods. Two other subjects, Subject No. 2 and Subject No. 5, had parent to metabolite exposure ratios that were similar to those of slow metabolizers in one out of 4 periods. Subject No. 2 had an exposure ratio of 16% in Period 1 (Treatment A) and Subject No. 5 had an exposure ratio of 10% in Period 2 (Treatment A). These exposure ratios were also substantially lower than those observed in other periods for these subjects. Additionally, plasma 3-OH DL concentrations for Subject No. 15 were below the LLOQ for Treatment A, Period 1 and the half-life was indeterminable for DL. This was not observed in any other treatment periods for this subject. The reason for the variability observed with these subjects is unknown; however, including these subjects in the assessment of bioequivalence did not impact the conclusions. Mean exposure to 3-OH DL (AUC [I]) was moderately variable following administration of either DL D-12 formulation. Mean AUC (I) CVs ranged from 33 to 34%. 3-OH DL was eliminated with a mean half-life (t½) of ~31 hours. Relative to the DL D-12 Phase 3 formulation, DL D-12 improved formulation met 80-125% bioequivalence criteria for 3-OH DL. The 90% CI for 3-OH DL

Cmax and AUC (I) values (Treatment B/A) were 94.6-107% and 93.3-105%, respectively. The within subject treatment variability for the log transformed Cmax was larger for the new formulation (Treatment B) with ratio of the CV equal to 1.42 (=0.161/0.113).

Pharmacokinetic Assessments for PSE:
The mean exposure to PSE exhibited low intersubject variability; mean CV for Cmax and AUC values ranged from 13 to 25%. PSE was eliminated with a mean t½ of ~7-8 hours. Relative to the DL D-12 Phase 3 formulation, DL D-12 improved formulation met 80-125% bioequivalence criteria for PSE. The 90% CI for PSE Cmax and AUC (I) values (Treatment B/A) were 97.6-109% and 99.3-115% respectively. The within subject treatment variability for the log-transformed AUC(tf) and AUC(I) values were larger for the old formulation (Treatment A) with ratios of the CV equal to 1.61 (=0.175/0.109) and 1.59 (=0.178/0.112), respectively. However, the variation was not large enough to impact the bioequivalence of each of the two treatments.

Table. Summary of pharmacokinetic parameters calculated with all subjects:

Table 34 Treatment Ratios and Confidence Intervals for DL, 3-OH DL, and PSE

Protocol No. P02040

Parameter	Treatment B/Treatment A							
	n_A	lsmean A[a]	σ_{WA}[b]	n_B	lsmean B[a]	σ_{WB}[b]	Ratio[c]	90% CI[c]
	DL (All Subjects)							
Cmax	20	0.991	0.117	20	1.02	0.175	103	97.5 - 109
AUC(tf)	20	26.5	0.297	20	24.7	0.310	93.2	83.2 - 104
AUC(I)	19	26.0	0.276	19	24.9	0.321	95.9	85.1 - 108
	3-OH DL (All Subjects)							
Cmax	18	0.329	0.113	18	0.326	0.222	99.1	91.0 - 108
AUC(tf)	20	8.46	0.142	20	7.74	0.146	91.6	78.4 - 107
AUC(I)	20	14.8	0.128	20	14.7	0.123	99.0	91.0 - 108
	PSE (All Subjects)							
Cmax	20	251	0.120	20	261	0.115	104	98.9 - 109
AUC(tf)	20	4058	0.173	20	4457	0.137	110	103 - 117
AUC(I)	20	4182	0.174	20	4605	0.138	110	103 - 117

a: Least squares mean from ANOVA.
b: Treatment within subject variability.
c: Ratio and 90 percent confidence interval (CI) of treatment ratio.
Treatment B: DL D-12 (to be marketed formulation).
Treatment A: DL D-12 (Phase 3 formulation).

Conclusions:
Both treatments were safe and well tolerated. The DL D-12 improved formulation was bioequivalent to the DL D-12 Phase 3 formulation based on the bioequivalence assessment for PSE, DL and its major metabolite 3-OH DL. Bioequivalence has been demonstrated for both, DL and PSE, nevertheless the study has a number of deficiencies: the washout period was too short, and four subjects were removed from bioequivalence evaluations. On the other hand calculation of pharmacokinetic parameters with all subjects still showed bioequivalence. In this pivotal study a number of interindividual variabilities have been found. A detailed analysis of these outliers was performed, submitted and positively evaluated.

Study P02042:
The objective of this study was to determine the pharmacokinetics of DL, 3-OH DL, and PSE following single-dose administration of DL D-12 under fed and fasted conditions in healthy adult subjects. Twenty subjects between the ages of 18 and 44 years were enrolled in this single-dose, open-label, 2-way crossover study, 19 completed. Each subject was randomized to receive the following two treatments in a computer-generated sequence: One DL D-12 tablet was administered after a 10-hour fast (Treatment A), and one DL D-12 tablet was administered immediately following a

standardized high-fat, high-calorie breakfast (Treatment B). A washout period of 12 days separated the two treatment periods. Blood samples were collected for determination of the plasma pharmacokinetic profile of DL, 3-OH DL, and PSE for up to 120 hours. Plasma samples were assayed for DL, 3-OH DL, and PSE. DL pharmacokinetic parameters exhibited moderate inter-subject variability with CV values for Cmax and AUC (I) ranging from 41-49%. The corresponding values for 3-OH DL and PSE were 26-36% and 21-28%, respectively. Preliminary statistical analysis was performed to examine the extreme pharmacokinetic values and the impact of outliers on the overall results. Subject No. 17 met the outlier criterion for DL Tmax only, but not for Cmax or AUC. This subject was not an outlier for Cmax and AUC of 3-OH DL and PSE. Therefore, no additional analyses were done and the subject was included in all statistical displays. A method has been established to separate slow metabolizers from normal metabolizers based on the AUC ratio of 3-OH DL to that of DL. The ratio of 10% is used as the criterion to identify slow metabolizers. None of the 20 subjects were slow metabolizers of 3-OH DL, based on their AUC ratio values. Statistical comparisons of Cmax and AUC (I) values for fed versus fasted conditions were performed for DL, 3-OH DL, and PSE. The powers to detect a 20% difference in treatment means at an alpha-level of 0.05 (two-tailed) for the log-transformed DL, 3-OH DL, and PSE Cmax and AUC(I) values were 96 and 99, 99 and 100, and 100 and 100%, respectively. The 90% confidence intervals for the ratio of the log-transformed Cmax and AUC for DL, 3-OH DL, and PSE were all within the bioequivalence interval of 80% to 125%. Therefore, food had no effect on the bioavailability of DL, 3-OH DL, and PSE from the DL D-12 tablet. Study P02042 conducted with the improved formulation also showed no effect of food on the oral bioavailability of the DL D-12 tablet.

Study P02041:

The objective of this study was to determine the steady-state pharmacokinetic profile of DL, 3-OH DL, and PSE following twice-daily administration of the DL D-12 tablet (formula 3775) for 14 consecutive days. Eighteen healthy subjects between the ages of 22 and 45 years were enrolled in this multiple-dose, open-label study. Each subject received one DL D-12 tablet twice daily for 14 days. Blood samples were collected prior to dosing on Day 1 and prior to both morning and evening dosing on Days 10, 11, 12, and 13, and then on Day 14 for up to 24 hours after the morning dosing. Plasma concentrations of DL, 3-OH DL, and PSE were determined using validated liquid chromatography with tandem mass spectrometric methods. There was a statistically significant difference ($P<0.001$) in the mean Cmin (prior to the AM dose, 0 hour) values of DL and 3-OH DL over the period of Days 10 to 14. However, there was no consistent trend in the fluctuations of the individual or mean trough plasma concentrations. The 95% confidence intervals of the ratios fell within the interval 0.8 to 1.25, indicating that the differences between the Cmin concentrations were not clinically relevant. Therefore, steady-state plasma DL and 3-OH DL concentrations were attained by Day 10. For PSE, there was no statistically significant difference ($P=0.1$) or trend in the mean Cmin (prior to the AM dose, 0 hour) values over the period of Days 10 to 14, and the 95% confidence interval of the ratios fell within the interval 0.8 to 1.25. Steady-state conditions for plasma PSE concentrations were attained by Day 10 of multiple-dose administration of the DL D-12 tablet. For the Period 0-12 hour, the mean Cmax and AUC (0-12 hr) values of DL were approximately 1.7 ng/mL and 16 ng·hr/mL, respectively. The mean Tmax was approximately 3.9 hours. The mean Cmax and AUC (0-12 hr) of PSE were 459 ng/mL and 4658 ng·hr/mL, respectively. The mean Tmax was approximately 4.6 hours. Comparable results were obtained for the Period 12-24 hour. In conclusion, steady-state conditions were attained by Day 10 for DL, 3-OH DL, and PSE following multiple dosing of the DL D-12 tablet. According to the study above with the final formulation steady-state conditions were reached on Day 10. This difference has no clinical relevance.

Study P02043:

The improved formulation (3775) of the DL D-12 tablet used in clinical trials described above and the commercial use formulation were manufactured by different companies. In accordance with the EMEA "Guidance on the investigation of bioavailability and bioequivalence", the bioequivalence of the DL D-12 tablets manufactured at the two sites is supported by an *in vitro/in vivo* correlation (IVIVC) analysis. In cases where the bioavailability of the product undergoing change has been investigated and an acceptable correlation between *in vivo* performance and *in vitro* dissolution has been established, the requirements for *in vivo* demonstration of bioequivalence can be waived if the dissolution rate *in vitro* of the new product is similar to that of the already approved medicinal product

under the same test conditions as used to establish the correlation. The objectives of this single-dose study were to evaluate the bioequivalence of PSE from DL/PSE formulations with fast and slow dissolution rates relative to each of the standard formulations, as well as the bioequivalence of PSE from the standard formulations. These data were used to support an IVIVC analysis to establish an *in vitro/in vivo* correlation (IVIVC) between the *in vivo* absorption rate (percent of dose absorbed) and the *in vitro* release rate (percent of dose released) for four PSE extended release formulations. This study evaluated the pharmacokinetics of PSE from DL/PSE formulations with modified cores, which demonstrated very fast, fast, and slow dissolution rates relative to the DL D-12 standard formulation. Twenty subjects between the ages of 27 and 44 years (mean = 37.4 years) were enrolled in this single-dose, open-label, 4-way crossover study. Two formulations of the DL D-12 (standard and slow batches) and two formulations of the DL 5/120 (standard and fast batches) were administered in a random order to each of the 20 subjects following an overnight fast. The DL 5/120 standard batch had a modified core with a fast dissolution rate compared with the DL D-12 standard formulation. A washout period of 7 days was observed between each treatment. Blood samples for determination of PSE were collected for up to 48 hours after dosing. Plasma samples were assayed for PSE concentration using a validated LC-MS/MS method.

The DL D-12 standard batch was bioequivalent to the DL 5/120 standard batch with respect to the PSE component. The DL D-12 slow batch, but not the DL 5/120 fast batch, was bioequivalent to the DL D-12 standard batch with respect to the PSE component.

Table. Relative Bioavailability and 90% Confidence Intervals for the Log-Transformed Cmax, AUC Values of PSE Following Single-Dose Oral Administration of the DL D-12 or DL 5/120 Formulations (n=20)

Protocol No. P02043

Comparison	Parameter	Ratio (%)	90% CI
DL 5/120 Std/DL D-12 Std	AUC(tf)	104.2	99-110
	AUC(I)	104.7	99-110
	Cmax	111.8	107-117
DL D-12 Slow/DL D-12 Std	AUC(tf)	94.9	90-100
	AUC(I)	95.1	90-100
	Cmax	93.9	90-98
DL 5/120 Fast/DL D-12 Std	AUC(tf)	100.3	95-106
	AUC(I)	100.9	96-106
	Cmax	126.1	120-132

Std: standard.

In Vitro/In Vivo Correlation

An *in vitro/in vivo* correlation was developed for four formulations of PSE sulphate extended-release (DL D-12) tablets exhibiting different *in vivo* absorption and *in vitro* release characteristics. The *in vivo* bioavailability of these formulations was evaluated in 20 subjects under fasted conditions (P02043). Wagner-Nelson analyses of the *in vivo* data revealed the extended-release absorption profiles for all four formulations. Linear regression analyses of mean percent of dose absorbed vs. the mean *in vitro* percent of drug released resulted in statistically significant correlations (point to point) for each formulation. The in vitro release rate of PSE as a predictor of in vivo performance was achieved from developed IVIVC model for all formulations. These data support a Level A correlation between *in vivo* PSE absorption profile and *in vitro* release rates of four PSE extended release formulations determined in fasted healthy subjects.

Analytical methods

To support the clinical studies conducted with the DL D-12 tablet, liquid chromatographic/tandem mass spectrometric methods (LC-MS/MS) were developed and validated for quantitation of DL, 3-hydroxydesloratadine (3-OH DL, SCH 45581), and PSE in human plasma. The method for quantitation of DL and 3-OH DL used $^{2}H_{4}$-SCH 34117 and $^{2}H_{4}$-SCH 45581 as internal standards for

DL and 3-OH DL, respectively. The methods for quantitation of PSE used either amantadine or 1S,2R(+)Ephedrine-D_3 as an internal standard. In SN 99238, the method was cross validated for plasma collected with either EDTA or heparin as the anticoagulant. However, in the clinical studies, heparin was used as the anticoagulant; thus, the validation parameters are from validation runs in which heparin was the anticoagulant. All analytical methods met the requirements for specificity, sensitivity, accuracy, and precision. No endogenous matrix interference was observed at the retention times of the analytes or the internal standards. In addition, analyte stability was demonstrated under various storage and sample processing conditions.

- Special populations

- Genetic polymorphism
DL is extensively metabolized to 3-hydroxydesloratadine (3-OH DL), an active metabolite, which is subsequently glucuronidated. The enzyme(s) responsible for the formation of 3-OH DL have not been identified. Data from clinical trials with DL indicate that a subset of the general population has a decreased ability to form 3-OH DL, and are poor metabolizers of DL. In pharmacokinetic studies (n=3748), approximately 6% of subjects were poor metabolizers of DL (defined as subjects with area under the curve (AUC) ratios of 3-OH DL to DL less than 0.1, or subjects with DL half-lives exceeding 50 hours). The frequency of poor metabolizers in the adult subjects was higher in Blacks (18%) than in Caucasians (2%). Similar result was observed in the paediatric subjects (16% Blacks vs. 3% Caucasians). No safety issues have been identified with DL in poor metabolizers. Data pooled from various studies indicate that the safety profile of DL poor metabolizers is not different from that of the placebo group.

- Impaired renal/hepatic function
The pharmacokinetics of the DL D-12 tablet has not been evaluated in renally impaired or hepatically impaired patients. However, the pharmacokinetics of DL has been evaluated in such patients (see Original MAA DL-EMEA/H/C/310-314-Commission Decision: 15 JAN 2001). Due to the lack of data of PSE in these patients, the use of the DL D-12 tablet is not recommended in these patients.

- Gender
Sex has no clinically significant effect on the pharmacokinetics of the DL D-12 tablet. Data (weight-adjusted) pooled from eight Phase-1 studies, which included 183 subjects (77 women and 106 men between 18 and 45 years old), demonstrated no effect of sex on the pharmacokinetics of PSE from the DL D-12 tablet formulations. The ratios of the log-transformed AUC and Cmax values for the male subjects to those of the female subjects and the 90% confidence intervals of these ratios were within the 80%-125% bioequivalence limits.

- Race
The effect of race on the pharmacokinetics of the DL D-12 tablet was not evaluated. However, following 14 days of DL administration, the Cmax and AUC values for DL were 18% and 32% higher, respectively, in Blacks compared with Caucasians, probably due to a higher incidence of poor metabolizers in Blacks (3 Blacks were poor metabolizer compared with 1 Caucasian). For 3-OH DL, there was a corresponding 10% reduction in Cmax and AUC values in Blacks compared with Caucasians. These differences are not considered to be clinically relevant, and, therefore, no dose adjustment is recommended. The frequency of poor metabolizers in the adult subjects was higher in Blacks (18%) than in Caucasians (2%). Similar result was observed in the paediatric subjects (16% Blacks vs. 3% Caucasians). No safety issues have been identified with DL in poor metabolizers. Data pooled from various studies indicate that the safety profile of DL poor metabolizers is not different from that of the placebo group.

- Elderly
The dossier does not present pharmacokinetic data of the DL D-12 tablet investigated in an elderly population.

- Pharmacokinetic interaction studies

Drug interaction studies were not conducted with the DL D-12 tablet. However, for DL, drug interaction studies were conducted with erythromycin, ketoconazole, azithromycin, fluoxetine, and cimetidine. There was no clinically significant increase in the plasma concentration of DL and 3-OH DL, and no significant change in the safety profile of DL, as assessed by electrocardiogram (ECG) parameters, clinical laboratory tests, vital signs, and Aes. For the PSE component, the proposed SPC of the DL D-12 tablet will contain the standard drug interaction statements as stated in the harmonized SPC of loratadine /PSE.

Pharmacodynamics

Pharmacodynamic variables were not evaluated with the DL D-12 tablet in the clinical pharmacology program. However, the pharmacodynamic properties of DL tablet were extensively evaluated in the DL clinical program in adults. For the PSE component, the proposed SPC of the DL D-12 tablet will contain the standard pharmacodynamic properties as stated in the harmonized SPC of L/PSE. The pharmacodynamic properties of the DL D-12 tablet are expected to be similar to those of its components, DL and PSE.

- Conclusions on pharmacology

In conclusions, the BA/BE/PK studies with the DL 2.5 mg and PSE 120 mg Modified Release combination tablets were carried out according to internationally accepted guidelines regarding GCP, GLP and pharmacokinetic/statistical analysis of this type of data. The results of the various Phase-1 clinical studies (A/BE/PK) show that the final (to be marketed) DL D-12 tablet formulation is bio-equivalent to the formulation with which the safety and efficacy Phase-3 studies have been carried out. In addition, the results of two BA/BE studies showed that food has no effect on the bioavailability of the two active substances in the DL D-12 tablet. The results of biopharmaceutical studies showed no component interaction of the DL/PSE combination tablet, indicating that the pharmacokinetics of the individual components would be the same as that from the combination tablet. In addition, single and multiple dose studies showed no significant age- or gender-related influence on the pharmacokinetics of DL and 3-OH DL. The lack of significant drug-drug interactions on the pharmacokinetics of DL was shown in the original MAA for DL tablets. For the PSE component, the proposed SPC of the DL D-12 tablet contain the standard drug interaction statements as stated in the harmonized SPC of loratadine/PSE. No pharmacokinetic studies of the DL/PSE combination tablet were performed with hepatically or renally impaired patients. However, the pharmacokinetics of the DL tablet has been evaluated in such patients. The harmonized SPC of L/PSE does not recommend the use of it in patients with hepatic or renal impairment. Likewise, the SPC does not recommend the use of the DL/PSE combination tablet in such patients. The CHMP believed that the extent of clinical experience with DL and PSE makes the conduct of additional clinical trials investigating the pharmacokinetics of DL/PSE tablet in such patients unnecessary and unlikely to extend scientific knowledge in the subject area. The proposed SPC adequately reflects the actual scientific knowledge on DL and PSE for the relevant indications. According to the SPC 6% of the subjects in a series of pharmacokinetic and clinical trials had significantly higher plasma concentrations of DL. Some of these poor metabolizers had C_{max} values of DL approximately 3-fold higher and a plasma half-life, which was also approximately 3-fold longer than normal. It is now rather unusual that the enzyme(s) responsible for the biotransformation of an active substance has (have) not been identified. As mentioned in the SPC, this lack of information makes it difficult to predict/exclude certain interactions.

Clinical efficacy

- Main studies P00355 and P00362

The efficacy of the DL D- 12 tablet in the treatment of adolescent and adult subjects with SAR was evaluated in two identical Phase-3, multi-centre, randomised, active-controlled, double-blind, parallel-group studies (P00355 and P00362).

METHODS

Sample size and study participants

A total of 1,248 subjects were randomised to receive study treatment with DL D-12 BID, DL 5.0 mg QD, or PSE 120 mg BID (identical to the PSE in DL D-12) for 15 consecutive days. Both studies were conducted in adolescent and adult subjects (= 12 years of age) with SAR.

Treatments
To preserve blinding, a double-dummy technique was used. One placebo tablet was identical in appearance to the 5.0 mg DL tablet, and the other was identical to both of the DL D-12 plus 120 mg PSE tablets, which themselves were identical in appearance. Assigned study treatments were to be administered orally twice daily, approximately 12 hours apart and at approximately the same time each morning and evening, without regard for the timing of meals or other daily activities.
Objectives
To assess the efficacy and safety of the DL D- 12 tablet in the treatment of adolescent and adult subjects with SAR.
Outcomes/endpoints
The primary efficacy variables defined in the protocols were: (1) change from baseline in mean AM/ PM PRIOR 12 hours (how the subject felt over the previous 12 hours [reflective]) total symptom score excluding nasal congestion (from the diary) for the antihistamine component, and (2) change from baseline in mean AM/ PM PRIOR 12 hours nasal stuffiness/congestion score (from the diary) for the decongestant component.
Statistical methods
Efficacy: General descriptive statistics and two- way analyses of variance (ANOVA), which extracted sources of variation due to treatment and centre. Primary analyses were based on the all-randomised-subjects data set; confirmatory analyses of the primary efficacy variables were based on efficacy-evaluable subjects. Safety: Incidence of treatment- emergent adverse events, discontinuations due to adverse events, and changes from baseline in laboratory test results, vital signs, and electrocardiogram intervals were summarized and tabulated.

RESULTS
The primary efficacy variable for the antihistamine component in the SAR studies (P00355 and P00362) was the AM/PM PRIOR 12 hours total symptom score excluding nasal congestion (from the diary) over the 15- day treatment period expressed as the mean change from Baseline. The primary comparison for this variable was DL D- 12 versus PSE. Results of the analysis, with pairwise comparisons across the three treatment groups, are presented in Table 4.

Table 4 Total Symptom Score (Excluding Nasal Congestion) Analysis Results for Primary Endpoint (Days 1 to 15): Subject-Evaluated Mean AM/PM PRIOR 12 Hours

Protocol Nos. P00355 and P00362

Treatment Group	Baseline		Change from Baseline (Days 1 to 15)			DL D-12 Comparison
	N[a]	LS Mean[b]	N	LS Mean	%[c]	P-value
P00355						
DL D-12 BID (DL 2.5 / PSE 120 mg)	199	14.18	199	-6.54	-46.0	—
DL QD (5.0 mg)	197	14.82	197	-5.09	-33.5	<0.001
PSE BID (120 mg)	197	14.06	197	-5.07	-35.9	<0.001
P00362						
DL D-12 BID (DL 2.5 / PSE 120 mg)	213	15.19	213	-6.65	-43.0	—
DL QD (5.0 mg)	212	14.66	212	-5.35	-36.1	0.001
PSE BID (120 mg)	221	14.86	221	-5.28	-35.4	<0.001

a: Calculation of mean Baseline values included all subjects with Baseline and Endpoint data; calculation of mean post-Baseline values included all subjects with both Baseline and post-Baseline data at the specified time point(s).

b: LS (Least Square) Means are obtained from the two-way ANOVA model with treatment and site effects.

c: Mean percent changes are raw means.

The primary efficacy variable for the decongestant component in the two studies was the mean AM/ PM PRIOR 12 hours nasal stuffiness/ congestion score (from the diary) over the 15- day treatment period expressed as the mean change from Baseline. The primary comparison for this variable was DL D- 12 versus DL. Results of the analyses, including pairwise comparisons across the three treatments, are presented in Table 5.

Table 5 Nasal Stuffiness/Congestion Analysis Results for Primary Endpoint (Days 1 to 15): Subject-Evaluated Mean AM/PM PRIOR 12 Hours (All Randomized Subjects)

Protocol Nos. P00355 and P00362

Treatment Group	Baseline		Change from Baseline (Days 1 to 15)			DL D-12 Comparison
	N[a]	LS Mean[b]	N	LS Mean	%[c]	P-value
P00355						
DL D-12 BID (2.5 DL/120 PSE mg)	199	2.47	199	-0.93	-37.4	—
DL QD (5.0 mg)	197	2.50	197	-0.66	-26.7	<0.001
PSE BID (120 mg)	197	2.46	197	-0.75	-31.2	0.006
P00362						
DL D-12 BID (2.5 DL/120 PSE mg)	214	2.55	214	-0.92	-36.0	—
DL QD (5.0 mg)	213	2.56	213	-0.73	-28.9	0.005
PSE BID (120 mg)	221	2.56	221	-0.83	-31.8	0.167

a: Calculation of mean Baseline values included all subjects with Baseline and Endpoint data; calculation of mean post-Baseline values included all subjects with both Baseline and post-Baseline data at the specified time point(s).

b: LS Means are obtained from the two-way ANOVA model with treatment and site effects.

c: Mean percent changes are raw means.

In both studies, mean nasal congestion symptom scores (AM/PM PRIOR) were similar across the three treatment groups at Baseline. At the primary endpoint (Days 1 to 15), DL D- 12 was significantly (P= 0.005) more effective than DL in reducing nasal stuffiness/congestion. In Study P00355, mean percent reductions from Baseline in AM/ PM PRIOR nasal stuffiness/congestion symptom scores for Days 1- 15 were 37.4% and 26.7% for DL D- 12 and DL, respectively. Statistically significant improvement (P= 0.005) compared with DL was observed at all time points and time intervals as early as Day 2. In Study P00362,(2) mean percent reductions from Baseline in AM/ PM PRIOR nasal stuffiness/ congestion scores for Days 1 to 15 were 36.0% and 28.9% for DL D- 12 and DL, respectively. The DL D- 12 tablet was significantly more effective than DL in reducing nasal congestion as early as Day 1 of treatment. Mean and mean percent reductions from Baseline in AM/ PM PRIOR nasal stuffiness/congestion scores for Days 1 to 15, as well as statistical analysis results, were highly consistent between the two studies. The antihistaminic and decongestant efficacy of DL D- 12 at the end of the dosing interval were significantly greater than that of PSE and DL, respectively, over the 15- day treatment period, and were observed as early as Day 2 in both studies. Results of the analysis across the three treatment groups are presented in Table 6. In Study P00355, mean percent reductions from Baseline in AM/PM NOW total symptom scores, excluding nasal congestion, at the primary endpoint (Days 1 to 15) were 45.1% and 35.6% for DL D- 12 and PSE, respectively. In Study P00362 mean percent reductions from Baseline were 42.1% and 35.7% for DL D- 12 and PSE, respectively. The antihistaminic efficacy of DL D- 12 was significantly greater than that of PSE at the end of the dosing interval.

Table 6 Total Symptom Score (Excluding Nasal Congestion) Analysis Results for Primary Endpoint (Days 1 to 15): Subject-Evaluated Mean AM/PM NOW (All Randomized Subjects)

Protocol Nos. P00355 and P00362

Treatment Group	Baseline		Change from Baseline (Days 1 to 15)			DL D-12 Comparison
	N[a]	LS Mean[b]	N	LS Mean	%[c]	P-value
P00355						
DL D-12 BID (DL 2.5 / PSE 120 mg)	199	13.87	199	-6.27	-45.1	—
DL QD (5.0 mg)	197	14.75	197	-5.19	-35.2	0.011
PSE BID (120 mg)	197	13.82	197	-4.92	-35.6	0.001
P00362						
DL D-12 BID (DL 2.5 / PSE 120 mg)	213	14.84	213	-6.30	-42.1	—
DL QD (5.0 mg)	212	14.37	212	-5.19	-35.2	0.005
PSE BID (120 mg)	221	14.70	221	-5.28	-35.7	0.010

a: Calculation of mean Baseline values included all subjects with Baseline and Endpoint data; calculation of mean post-Baseline values included all subjects with both Baseline and post-Baseline data at the specified time point(s).

b: LS Means are obtained from the two-way ANOVA model with treatment and site effects.

c: Mean percent changes are raw means.

Overall, the results for subject- evaluated total symptoms, excluding nasal congestion, and nasal stuffiness/congestion scores for the PRIOR 12 hours and NOW time periods were similar to those observed for the primary PRIOR AM/ PM time period. In the opinion of the CHMP the two clinical trials are convincing and no additional questions are to be answered to be able to grant a marketing authorisation.

- Supportive studies

A search of the medical literature was conducted to identify any studies comparing DL plus PSE versus its components or placebo in the symptomatic treatment of allergic rhinitis. The terms used in the search were DL, PSE and placebo. No reference was identified comparing DL/PSE versus placebo, whereas one reference was identified comparing DL/PSE versus its components. This reference is based on one of our pivotal studies, P00362. Since no reference was identified comparing DL/PSE versus placebo, the literature search was extended to L plus PSE against placebo. The terms used in the search were L, PSE and placebo. Seven references were identified. All these references consistently show that the combination of L and PSE is more effective than placebo in relieving symptoms of allergic rhinitis, including nasal congestion.

- Conclusions on clinical efficacy

The efficacy of this fixed combination is comparable to the efficacy that has been seen with the other fixed combination L plus PSE.

Clinical safety

- Patient exposure

The safety of DL alone has been well established in clinical trials involving more than 6000 subjects and in post- marketing experience. In clinical trials, the adverse event (AE) profile of DL was similar to that of the placebo group. The safety of PSE, a widely used oral nasal decongestant, is well established when the agent is used at the recommended doses. PSE is available in many countries without a prescription. To support the clinical development of DL D- 12 tablet, two Phase- 3 and nine Phase- 1 studies were conducted. The two Phase- 3 studies and four of the nine Phase- 1 studies were conducted with original formulation of the DL D- 12 tablet. One additional study was conducted with the PSE core formulations (without DL). Subsequently, the original formulation was modified to improve on the stability of the tablet. With the modified formulation (final), four additional studies were conducted. The safety data of the DL D- 12 tablet presented in this document are derived from all these 11 studies. The two Phase- 3 studies (and were multi-centre, randomised, active- controlled, double- blind, and parallel- group studies, designed to evaluate whether DL D- 12 tablet BID provided greater symptomatic relief than either component alone, and to ascertain the safety profile of DL D- 12 relative to its components in subjects with SAR. All subjects were included in the safety evaluations: 414 received DL D- 12, 412 received DL, and 422 received PSE. Of these 1248 subjects, 83

discontinued the study prior to scheduled completion. Safety was evaluated by reviewing AEs, electrocardiograms (ECGs), vital signs, and laboratory results. Forty- four subjects discontinued because of AEs. Overall, the percentage of discontinuations was low in each treatment group: 6.0% in the DL D- 12 group, 5.1% in the DL group, and 8.8% in the PSE group. A total of 126 healthy volunteers were enrolled in the four Phase-1 studies that were conducted with the original formulation of the DL D- 12 tablet and the one study that was conducted with the PSE core formulations (without DL). Four were single-dose studies, and one was a multiple-dose study. Eight subjects discontinued from the studies; two because of AEs. Four studies were conducted with the final formulation of the DL D- 12 tablet. In these studies, a total of 78 healthy subjects were enrolled. One subject discontinued from the study for a reason not related to AEs. In the four Phase- 1 studies conducted with the original formulation of DL D- 12 and one study with the PSE cores, 126 subjects were enrolled. Of the 126 subjects, 73 received only DL D- 12, 36 received DL D- 12, 2.5 mg DL, and 120 mg PSE, and 17 received only PSE. Seventy- eight subjects were enrolled in the four studies conducted with the final formulation of the DL D- 12 tablet. Total patient exposure for patients treated with the DL D- 24 tablet is estimated from post market exposure data.

- Adverse events

Overall, the incidence of severe treatment- related AEs was very low across all treatment groups, occurring in ≤4.5% of subjects in any treatment group. The most frequently reported severe treatment-related AEs across treatments were insomnia and dry mouth, and were reported more frequently among subjects receiving DL D- 12 or PSE than those receiving DL. Insomnia and dry mouth are established potential adverse effects of PSE.

- Serious adverse event/deaths/other significant events

Severe AEs that occurred in more than one subject in any treatment group are presented in Table 11. The overall incidence of severe AEs was similar in subjects treated with DL D- 12 and PSE (7.7% and 9.2%), but was lower in subjects treated with DL (4.9%). Insomnia was reported in 1.4% and 2.4% of subjects in the DL D- 12 and PSE treatment groups, respectively. Headache was reported by 1.9% of DL D- 12 subjects, and dry mouth occurred in 1.0% of DL D- 12 subjects. Sinusitis occurred in 1.7% of PSE subjects. All other severe AEs were reported by < 1% of subjects in any treatment group.

Table 11 Severe Treatment-Emergent Adverse Events Reported by >1 Subject in Any Treatment Group, by Body System/Organ Class: Pooled Data From Studies P00355/00362 (All Randomized Subjects)

Body System/Organ Class Preferred Term	Number (%) of Subjects[a] DL D-12 2.5 DL/120 PSE mg BID (N = 414)	 DL 5.0 mg QD (N = 412)	 PSE 120 mg BID (N = 422)
Any Severe Adverse Event	**32 (7.7)**	**20 (4.9)**	**39 (9.2)**
Autonomic Nervous System Disorders	**4 (1.0)**	**0**	**4 (< 1)**
Mouth Dry	4 (1.0)	0	4 (< 1)
Body As a Whole - General Disorders	**10 (2.4)**	**4 (1.0)**	**7 (1.7)**
Headache	8 (1.9)	3 (< 1)	4 (< 1)
Central and Peripheral Nervous System Disorders	**3 (< 1)**	**0**	**3 (< 1)**
Dizziness	2 (< 1)	0	1 (< 1)
Gastrointestinal System Disorders	**4 (1.0)**	**3 (< 1)**	**4 (< 1)**
Anorexia	1 (< 1)	0	2 (< 1)
Nausea	1 (< 1)	1 (< 1)	2 (< 1)
Vomiting	0	2 (< 1)	1 (< 1)
Musculoskeletal System Disorders	**2 (< 1)**	**2 (< 1)**	**1 (< 1)**
Arthralgia	2 (< 1)	0	0
Psychiatric Disorders	**10 (2.4)**	**2 (< 1)**	**13 (3.1)**
Insomnia	6 (1.4)	1 (< 1)	10 (2.4)
Somnolence	3 (< 1)	0	0
Respiratory System Disorders	**2 (< 1)**	**6 (1.5)**	**8 (1.9)**
Pharyngitis	0	2 (< 1)	0
Sinusitis	0	1 (< 1)	7 (1.7)
Vision Disorders	**0**	**2 (< 1)**	**0**
Eyes, Dry	0	2 **(< 1)**	0

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

No deaths were reported in either the clinical efficacy and safety studies or the clinical pharmacology studies.

- Safety in special populations

In the Phase-3 studies (P00355 and P00362), the effects of age, race, and sex on the incidence of AEs were also investigated. In general, no substantial difference in the pattern of AEs among treatment groups was evident in any of the demographic subgroups. The overall incidence and pattern of AEs in the subgroups was consistent with that observed in the overall population. There were too few subjects ages 12 to <18 years and ≥65 years or who were non-Caucasians to make any formal comparisons with respect to age or race. According to the SPC of L/PSE tablets the combination should not be administered to patients above 60 years of age as there are insufficient data concerning efficacy, safety and dose recommendations in this group and further patients of 60 years or older are more likely to experience adverse reactions to sympathomimetic medications. These facts are also valid for the DL/PSE tablet and are reflected in the SPC. Additional explanations provided by the applicant reassured the CHMP that the experience from the single components as well as data from L/PSE combination indicate that DL D- 12 is safe and effective in treatment of the symptoms of allergic rhinitis, including congestion, in subjects 12 to <18 years old similar to the adult subjects.

- Safety related to drug-drug interactions and other interactions

In the single-dose Phase-1 studies (P02042) food did not significantly alter the safety profiles of either formulation of DL D-12 tablets when the formulations were administered with or without food. In Study P02042, none of the subjects in the fasted state, and three subjects in the fed state reported AEs. The effects of concomitant medications, tobacco, and alcohol on the safety profile of DL D-12 were not evaluated in this submission. Drug interactions were not evaluated in this submission. However, previous studies have indicated that DL (one of the components of DL D-12) may be safely co-administered with azithromycin, cimetidine, erythromycin, and ketoconazole. On the basis of the

pharmacological effects and the available clinical data for PSE, no significant interaction is expected when PSE is administered concomitantly with the above drugs. The proposed SPC of the DL D-12 tablet will contain the standard drug interaction statements of PSE as stated in the harmonized SPC of L/PSE.

- Post marketing experience

The applicant currently markets two strengths of the DL/PSE combination tablets; DL D-12 tablet (approved on 1 FEB 2006) and DL D-24 tablet (3 MAR 2005). The DL D-24 tablet contains 5 mg of DL and 240 mg of PSE (once-daily daily). Both tablets are available only in the USA. Since the DL D-12 tablet was recently marketed, no exposure data are available, and as of 31 MAR 2006, no post-marketing AEs were reported to the Global Pharmacovigilance Department (GPV) of the applicant. Adverse events presented in this section consist of all spontaneous and literature reports reported to GPV with the DL D-24 tablet during the period of 3 MAR 2005 to 31 MAR 2006.

- Conclusions on clinical safety

The safety profile of this fixed combination seems to be very comparable with that of the ones on the market. No new signal has been picked up.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP did not require the MAA to submit a risk management plan because both components are already well known and long-term on the market and no important safety concerns have been so far identified.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the product 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. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology
For a fixed combination containing compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95). This is the case for the DL/PSE combination, since sufficiently documented human experience is available for the L/PSE combination. In addition, a comparison between the newly submitted DL studies and the previously submitted studies with L was made. The non-clinical safety profiles of L and DL are similar. DL/PSE is considered unlikely to represent a risk for the environment following its prescribed usage in patients.

Efficacy
The efficacy of the DL D-12 tablet in the treatment of adolescent and adult subjects with SAR was evaluated in 2 identical Phase-3, multi-centre, randomised, active-controlled, double-blind, parallel-group studies (P00355 and P00362). A total of 1,248 subjects were randomised. Both studies were conducted in adolescent and adult subjects with SAR. The efficacy of this fixed combination is comparable to the efficacy that has been seen with the other fixed combination L plus PSE. The two

clinical trials are convincing and no additional questions are to be answered to be able to grant a marketing authorisation. Additionally, a search of the medical literature was conducted to identify any studies comparing DL plus PSE and L plus PSE versus its components or placebo in the symptomatic treatment of allergic rhinitis. The data presented in this submission demonstrate that the DL D-12 combination tablet is safe and more effective than either component alone in relieving the symptoms of SAR, including nasal congestion.

Safety
The safety of DL alone has been well established in clinical trials involving more than 6000 subjects and in post-marketing experience In clinical trials, the AE profile of DL was similar to that of the placebo group. The safety of PSE, a widely used oral nasal decongestant, is well established when the agent is used at the recommended doses. PSE is available in many countries without a prescription. The safety data of the DL D-12 tablet presented in this document are derived from all these 11 studies. The most frequently reported severe treatment-related AEs across treatments were insomnia and dry mouth, and were reported more frequently among subjects receiving DL D-12 or PSE than those receiving DL. Insomnia and dry mouth are established potential adverse effects of PSE. The safety profile of this fixed combination seems to be very comparable with that of the ones on the market. No new signal has been picked up. From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the SPC.

- User consultation

The applicant undertook to submit the results of the readability testing on the product information as a post authorisation commitment.

Risk-benefit assessment

- The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Aerinaze in the symptomatic treatment of seasonal allergic rhinitis when accompanied by nasal congestion was favourable and therefore recommended the granting of the marketing authorisation .