ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS / MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria		Lictyn 10 mg – Tabletten	10 mg	Tablet	Oral use
Bulgaria		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Loratadin Sandoz	10 mg	Tablet	Oral use
Czech Republic		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Loratadin Sandoz 10 mg tablety	10 mg	Tablet	Oral use
Denmark	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria		LORATADIN SANDOZ	10 mg	Tablet	Oral use
Estonia		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Lomilan	10 mg	Tablet	Oral use
Finland	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria		LORATADIN SANDOZ 10 MG	10 mg	Tablet	Oral use
France		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Loratadine SANDOZ CONSEIL 10 mg comprimé	10 mg	Tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Sandoz Pharmaceuticals GmbH Raiffeisenstr. 11 D-83607 Holzkirchen Germany		LORATADIN SANDOZ 10 MG TABLETTEN	10 mg	Tablet	Oral use
Greece	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria		TIRLOR	10 mg	Tablet	Oral use
Hungary		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Loratadin Sandoz 10 mg tabletta	10 mg	Tablet	Oral use
Italy		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	LORATADINA HEXAL AG 10 mg compresse	10 mg	Tablet	Oral use
Latvia		Sandoz B.V. Verovskova 57 SI-1000 Ljubljana Slovenia	Lomilan 10 mg tabletes	10 mg	Tablet	Oral use
Lithuania		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Lomilan	10 mg	Tablet	Oral use
Netherlands	Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands		Loratadine Sandoz 10, tabletten 10 mg	10 mg	Tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Norway	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria		LORATADIN SANDOZ 10 MG	10 mg	Tablet	Oral use
Poland		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Flonidan tab	10 mg	Tablet	Oral use
Portugal	Sandoz Farmacêutica, Lda. PRT Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra		LORATADINA SANDOZ 10 MG COMPRIMIDOS	10 mg	Tablet	Oral use
Romania		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Loratadina SANDOZ 10 mg comprimate	10 mg	Tablet	Oral use
Slovak Republic		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Flonidan 10 mg tablety	10 mg	Tablet	Oral use
Slovenia		Sandoz B.V. Veluwezoom 22 1327 AH Almere The Netherlands	Florin 10 mg tablete	10 mg	Tablet	Oral use
Spain	Sandoz Farmacéutica, S.A. Gran Via de los Corts Catalanes, 764 08013-Barcelona Spain		LORATADINA GENPRIL 10 MG COMPRIMIDOS EFG	10 mg	Tablet	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria		LORATADIN SANDOZ 10 MG	10 mg	Tablet	Oral use
United Kingdom	Sandoz Limited Woolmer way Bordon, Hants, GU35 9 QE United Kingdom		LORATADINE 10 MG TABLETS	10 mg	Tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR NEGATIVE OPINION

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LORATADINE SANDOZ 10 AND ASSOCIATED NAMES (SEE ANNEX I)

Loratadine is an antagonist of histamine at H1 receptor sites (competitive, reversible) leading to the relief of allergic symptoms. Loratadine is a potent, long acting antihistaminic which has a high selectivity for peripheral histamine H1-receptors and low affinity for H1-receptors in the central nervous system (CNS) in vitro or in vivo. Histamine is a major mediator of the allergic reaction. In the clinical setting, loratadine has been used for over 10 years in the treatment of allergic disorders such as conjunctivitis, atopic dermatitis, urticaria, asthma, and anaphylaxis. The sought indications for Loratadine Sandoz 10 were the relief of symptoms associated with seasonal and perennial allergic rhinitis and the treatment of the symptoms of chronic urticaria. The Applicant submitted an application for a repeat use procedure of Loratadine Sandoz 10 and associated names, 10 mg tablets on the basis of the marketing authorisation granted by The Netherlands on 12 July 2001. Because major objections on bioequivalence remained unresolved, an Article 29(4) referral was triggered and the procedure was referred to the CHMP.

The calculated 90% CI for AUC0-t, AUCinf and Cmax for the metabolite descarboethoxyloratadine were within the 0.80- 1.25 acceptance range, but bioequivalence for loratadine tablets should also be based on parent compound data and because the 90% CI for Cmax and AUC of the parent compound were outside the standard 0.80 - 1.25 acceptance criterion, the objecting concerned member states considered that bioequivalence between Loratadine Sandoz 10 and the reference product could not be established. The Applicant was requested to provide the CHMP with the parent compound data from the submitted bioequivalence study or to provide satisfactory justifications for the absence of these data. The Applicant decided to perform a new BE study and submitted the full details of a single centre, randomised, single-dose, open-label, laboratory blinded 2-way crossover bioequivalence study comparing the rate and extent of absorption of Loratadine Sandoz 10 mg tablets versus the reference loratadine (Clarityne by Schering-Plough) under fasting conditions (Study SZ190/08). 80 subjects were enrolled in the study and randomly assigned to a treatment. Treatment phases were separated by a washout period of 21 days and subjects were administered a single oral dose as a 1 x 10 mg tablet and blood sampling was carried out prior to dosing (0) and at regular intervals post-dose. Loratadine and descarboethoxyloratadine concentrations in plasma were determined by s liquid chromatography assay with MS-MS detection. The validation process was described in detail and the study and the analyses were made in accordance with GLP principles as well as international regulatory recommendations and guidelines. No clinically significant abnormalities were observed and the results confirmed the absence of significant changes in the subjects' state of health. The following pharmacokinetic parameters were determined: AUC_{0-t}, C_{max} (primary) and AUC_{∞} residual area, t_{max}, $K_{e;}$, $t_{1/2}$ (secondary). Regarding the basic statistical parameter analysis of AUC∞, AUCt and Cmax, both AUCs and Cmax values were subjected to analysis of variance (ANOVA), following the logarithmic transformation. For parametric analysis, the 90% confidence interval was calculated.

The CHMP noted that the study site had been satisfactorily inspected and that the study was performed according to GCP guidelines. The study was considered acceptable for the estimation of PK parameters and properly designed in terms of wash-out, sampling periods and drug intake procedures. The CHMP also noted the statement on GLP compliance in bio-analysis and considered that the analytical methods are acceptable and validated appropriately and seem adequate to accurately determine the concentration of loratadine and descarboethoxyloratadine in plasma. The samples were handled adequately and plausible reasons were presented for analysis repetition. The CHMP also considered that the choice of pharmacokinetic variables was adequate for this study and that the pharmacokinetic calculation was presented correctly. The statistic analysis was described adequately, and the methods for statistical assessment of this bioequivalence study were acceptable.

Regarding the results, the Applicant provided the pharmacokinetic parameters for loratadine and for descarboethoxyloratadine as well as all the individual plasma concentrations, pharmacokinetic variables and

individual graphs. A total of 30 post-dose adverse events were reported, with 6 adverse events probably related to the study treatment, 11 possibly related, 2 remotely related, and 11 unrelated. The majority of adverse event were considered mild and the most commonly reported was headache (8.8% of subjects). In conclusion, the submitted study demonstrates the bioequivalence of Loratadine Sandoz 10mg tablets to the reference product for AUC_{0-t} and $AUC_{0-\infty}$ of loratadine, but not for the C_{max} parameter. The Applicant considered that due to the large intra-subject variability of loratadine, the use of a wider CI (0,75 – 1,33) was justified, and that differences in C_{max} do not have a major clinical effect on the use of this product in humans. Additionally, the results for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of descarboethoxyloratadine demonstrated bioequivalence. The Applicant, taking into account the lack of serious safety or efficacy concerns, therefore concluded that Loratadine Sandoz 10 can be considered to be efficacious and safe.

The CHMP noted the presented data and stated that according to the current guideline (Questions & Answers on the Bioavailability and Bioequivalence Guideline CHMP/EWP/40326/06), bioequivalence should preferably be based on data for the parent drug, loratadine, as confirmed in the most recent draft guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). The data showed that for loratadine, the 90% confidence interval for C_{max} is outside the predefined acceptance range of 80-125% (although the 90% confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$ were respected). According to the guideline, a wider interval may be acceptable, but only if prospectively defined and justified, addressing in particular any safety or efficacy concerns for patients switched between formulations. A post hoc justification for widening the acceptance range as was done for study SZ190/08 can therefore not be accepted. The CHMP concluded that the bioequivalence between Loratadine Sandoz 10 and the reference product was not sufficiently demonstrated and adopted a List of Outstanding Issues, requesting the Applicant to further substantiate bioequivalence.

The Applicant emphasised that bioequivalence was shown for the metabolite, which is responsible for the main effect. Detailed explanations of the statistical calculations and the improved bio-analytical methods used were provided and in addition, the Applicant explained that the pharmacokinetics of loratadine increased its intra-individual variability. This increase justifies either an additional increase of subjects included in the study or a widening of the acceptance criteria. Loratadine Sandoz 10 is used for the long term treatment of allergies and both parent compound and metabolite contribute to the clinical efficacy. Treatment with H_1 – antagonists for the sought indication requires sufficient therapeutic drug levels for a period superior to 24 hours in order to provide relief from symptoms and the Applicant therefore argued that the therapeutic effect is best represented by the AUC of the unchanged loratadine and the metabolite rather than the peak concentration of parent compound alone. In addition, Sandoz pharmacovigilance database indicates that there are no unaddressed safety or efficacy concerns for Loratadine Sandoz 10.

The CHMP confirmed that the Guideline and the Q&A document (which were valid and available on the EMEA website at the time when the protocol for the bioequivalence study was finalized) state that a retrospective widening of the acceptance criteria for Cmax results is not allowed. Therefore, in view of the results obtained from the original study, demonstrating an intra-individual CV of 41.2% for Cmax, a widening of the confidence interval should have been predefined in the study protocol of the second study (justifying any safety or efficacy concerns for patients switched between formulations). The arguments used by the Applicant that the increase of about 5% in the intra-individual variability of Cmax in the second study (CV of 46.4%) justifies the post-hoc widening of the acceptance criteria cannot be accepted. This situation should have been foreseen and included in the study protocol and the CHMP therefore considers this to constitute a major objection. The guidelines state that "In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite". The metabolite can be used as a surrogate only if the Applicant presents convincing arguments demonstrating that it is not possible to reliably measure the parent compound after a single administration, which is not the case for loratadine.

The Applicant requested an oral explanation in front of the committee in order to discuss the outcome of the CHMP assessment. The Applicant assumption that the parent compound is inactive was not accepted, as the

absolute activity should be taken into account, rather than the ratio of activity compared to the metabolite. In order to consider the parent compound as inactive, a significantly lower level of activity would have been required. The data available shows that the parent compound is measurable, and therefore must be measured, in order to assess bioequivalence. It was concluded that any arguments for the widening of the acceptance range must be discussed prospectively, and reflected in the protocol.

While bioequivalence between Loratadine Sandoz 10 and the reference product was shown for the active metabolite, bioequivalence with regards to the parent compound was not demonstrated. According to the current applicable guidelines, bioequivalence must be demonstrated for the parent compound for generic products. Therefore, the products cannot be considered bioequivalent and the CHMP concluded that the benefit-risk of Loratadine Sandoz 10 is negative. In addition, the widening of the Confidence Intervals should be agreed prospectively in the study design.

GROUNDS FOR NEGATIVE OPINION

Whereas

- retrospective widening of the confidence interval is not accepted according to the current guidelines,

- bioequivalence between Loratadine Sandoz 10 and the reference product was not demonstrated for the parent compound,

the benefit-risk of the generic Loratadine Sandoz 10 is therefore considered to be negative,

the CHMP has recommended the refusal of the granting of the Marketing Authorisations in the Concerned Member States and the suspension of the Marketing Authorisation in the Member States where the product is currently authorised, for Loratadine Sandoz 10 and associated names (see Annex I).

ANNEX III

CONDITIONS FOR THE LIFTING OF THE MARKETING AUTHORISATION SUSPENSIONS

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holder(s):

The Applicant should submit the results of a correctly planned study that demonstrates the bioequivalence between Loratadine Sandoz 10 and the reference product in accordance with the current guidelines.