Annex I

List of the names, pharmaceutical form, strength 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
Czech Republic		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans 10 mg tablety	10 mg	tablet	oral use
Denmark		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loraxin	10 mg	tablet	oral use
Estonia		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans	10 mg	tablet	oral use
Finland	Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland		Loraxin	10 mg	tablet	oral use
Hungary		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loraxin	10 mg	tablet	oral use
Latvia		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans 10 mg tabletes	10 mg	tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Applicant	(Invented) Name	Strength	Pharmaceutical form	Route of administration
Lithuania		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loraxin	10 mg	tablet	oral use
Norway		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans	10 mg	tablet	oral use
Poland		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans	10 mg	tablet	oral use
Slovak Republic		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans 10 mg	10 mg	tablet	oral use
Slovenia		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans 10 mg tablete	10 mg	tablet	oral use
Sweden		Vitabalans Oy Varastokatu 8 13500 Hämeenlinna Finland	Loratadine Vitabalans	10 mg	tablet	oral use

Annex II

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Loraxin and associated names (see Annex I)

Loratadine is a second-generation long-acting, non-sedating antihistamine with no significant antimuscarinic activity. Loraxin 10 mg is a conventional compressed immediate release tablet with loratadine as the active substance. Loratadine was first authorised as Claritine 10mg tablet in Belgium, since 1987.

The mutual recognition marketing authorisation application presented for the medicinal product Loraxin 10 mg tablets is a well-established use (WEU) application according to Article 10a of Directive 2001/83/EC. The application for Loraxin is therefore based on publicly available bibliographic data as it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognized efficacy and an acceptable level of safety.

The use of loratidine is wide in clinical practice and a number of published papers have been submitted in support of efficacy and safety. For the majority of the clinical studies referenced in the submitted literature, the product was not clearly defined. These studies include loratadine products in several strengths from 5 mg up to 40 mg. The intended daily dosage of Loraxin is 10 mg. In these studies pharmacokinetic parameters have been studied after single dose as well as after 10 days (40 mg/day) administration of loratadine. The populations studied have been healthy adult volunteers as well as children and renal impairment patients.

Part II.1.d) of Annex I of Directive 2001/83/EC is states that " the non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product for which application for marketing authorisation has been made in spite of existing differences".

In order to show the relevance of the bibliographic data used in support of the application for Loraxin, the MAH referred to pharmaceutical, pharmacokinetic and clinical data.

- Pharmaceutical data

The MAH's argument that the literature on the originator product is relevant for their product on the basis of the submitted pharmaceutical data is not considered scientifically valid by CHMP. Loratadine is not a BCS class I (high solubility-high permeability) or III ((high solubility-low permeability) substance, which might otherwise have supported an extrapolation based on the pharmaceutical data. Instead, as it is a BCS class II (low solubility-high permeability) or IV (low solubility-low permeability) substance additional data would be needed to support the relevance of the bibliographic data to demonstrate efficacy and safety of Loraxin.

- Pharmacokinetic data

The report of a pharmacokinetic study (Report V-808) submitted by the MAH in support of the marketing authorisation application was considered by the CHMP, since the inclusion of pharmacokinetic data in support of a well-established use application could be considered, if it is intended to show the relevance of the literature used to demonstrate safety and efficacy as regards the product concerned. This study was a two period cross-over bioequivalence study with only 40 subjects (in total 80 separate drug intake events).

The results show that the 90% confidence interval of the AUC_t (0.727-0.967) and C_{max} (0.727-0.945) of the test product (Loraxin) to the product Clarityn did not conform to the acceptance interval of 0.8-1.25. Although the 90% confidence interval of the AUC_t (0.884-1.035) and C_{max} (0.822-0.989) of the metabolite desloratadine were within the acceptance interval, the CHMP considered that the pharmacokinetic data did not support the submitted bibliographic data since the evaluation of bioequivalence should in principle be based upon measured concentrations of the parent compound (in this case loratadine and not desloratadine). More importantly, the sensitivity of the assay was considered to be insufficient to detect low concentrations of the parent compound (and the main metabolite desloratadine). The lower limit of detection in the analytical method used was 0.2 ng/ml, and due to this, over 50% of the plasma samples loratadine/desloratadine concentrations were below the lower limit of quantification and could not be determined. Therefore the CHMP was of the view that the submitted pharmacokinetic study report V-808 did not confirm the relevance of the bibliographic data submitted to demonstrate safety and efficacy of Loraxin.

- Clinical data

With regard to the additional clinical data to support the efficacy and safety of Loraxin, the MAH has submitted two expert reports. However one of the reports does not contain any data regarding PK/PD (or dose-response) relationships. Although the other report contained some information on dose-response this only referred to urticaria. Therefore the CHMP considered the provided clinical data to be very limited and not strong enough to address what a potential difference in exposure, compared to the exposure obtained following administration of the product used in the pivotal clinical studies described in the submitted bibliography, could mean for efficacy and safety for each indication.

Overall conclusion

In view of the above, the CHMP considered that the pharmaceutical, pharmacokinetic and clinical data/documentation referred to by the MAH was not considered sufficient to establish the relevance of the bibliographic data to Loraxin.

Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the June 2012 CHMP meeting, a request for re-examination was received from the MAH Vitabalans Oy on 6 July 2012 and the detailed grounds were submitted on 31 August 2012. The MAH also presented their grounds at an oral explanation on 16 October 2012.

The MAH expressed its disagreement on some procedural aspects of the mutual recognition procedure, the CMDh procedure and the referral procedure under Article 29(4) of Directive 2001/83/EC.

However, it is noted that the CHMP is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the referral procedure under Article 29(4) of Directive 2001/83/EC focussed only on the scientific points addressed in the grounds for re-examination.

The MAH expressed its disagreement with the CHMP opinion, focusing its scientific grounds on the following points, for which the MAH argues that clear justifications or evidence have not been presented to explain:

☐ why the applied loratadine 10 mg product would cause a potential serious risk to public health

☐ how the applied loratadine 10 mg product would cause a potential serious risk to public health

As mentioned previously, Annex I of Directive 2001/83/EC states that the non-clinical and/or clinical overviews must explain the relevance of any data submitted in relation to the product under application. Therefore, a scientifically valid approach such as the demonstration of comparable kinetics may be necessary to bridge Loraxin to a similar product.

In addition it is also noted that according to the Guideline on the Definition of a Potential Serious Risk to Public Health, a potential serious risk to public health in relation to a particular medicinal product can be considered to exist if the data submitted to support therapeutic efficacy do not provide sound justification for the claims of efficacy and/or the clinical safety data does not provide adequate support for the conclusion that all potential safety issues have been appropriately and adequately addressed.

During the re-examination procedure, the MAH did not demonstrate adequately that the published literature of loratadine is directly applicable to Loraxin. As discussed previously a pharmacokinetic study was provided to bridge Loraxin to the published literature and the AUC_t and C_{max} of Loraxin to the product Clarityn did not conform to the acceptance interval of 0.8-1.25 for the parent compound, loratadine.

Re-examination of these data and also taking into account the two expert reports submitted by the MAH, confirmed that the results of the pharmacokinetic study are not reliable for loratadine. In several plasma samples the concentration of loratadine was below the lowest level of quantification (LLOQ). Furthermore, there were extensive inter-subject variabilities in the absorption parameters of loratadine.

Based on the pharmacokinetic study results used to bridge Loraxin to the published literature, there is a potential for difference in exposure after Loraxin administration as compared to the product Clarityn, and the MAH has not adequately justified why this potential difference in exposure is unlikely to have a clinically significant difference in efficacy or safety.

The experts reports submitted during the referral procedure suggest that that there could be a slightly lower exposure to loratadine, based on the results of the supportive pharmacokinetic study provided by the MAH. However the case for a lack of significant difference in efficacy concerns due to lower exposure is not adequately addressed in both the expert reports.

Overall, the CHMP was still of the view that due to its limitations, the study could not confirm the relevance of the bibliographic data submitted to demonstrate safety and efficacy of Loraxin.

It is also noted that the case for the safety concerns due to potentially higher exposures has not been adequately addressed by the MAH.

Based on the published literature and the pharmacokinetic study results used to bridge Loraxin to the published literature, the relevance of the literature data submitted which concern a product different from the product intended for marketing was not addressed satisfactorily. As it could not be established whether a potentially lower or higher exposure to loratidine compared to the exposure obtained following administration of the product used in the pivotal clinical studies described in the submitted literature would constitute any efficacy or safety concerns, the CHMP therefore maintained its concern that this is a potential serious risk to public health.

Grounds for refusal

On the basis of the bibliographic data submitted, taken together with the pharmaceutical, pharmacokinetic and clinical documentation, the MAH failed to establish the relevance of these data to demonstrate safety and efficacy of Loraxin.

Whereas

- The Committee considered the notification of the referral triggered by Finland under Article 29(4) of Council Directive 2001/83/EC. Sweden and Poland considered that the granting of the marketing authorisation constitutes a potential serious risk to public health**.**
- The data referred to by the MAH is not considered sufficient to address what a potential difference in exposure, compared to the exposure obtained following administration of the product used in the pivotal clinical studies described in the submitted bibliography, could mean for efficacy and safety for each indication.
- the provided data does not show that Loraxin is similar to the product used in the pivotal clinical studies described in the submitted bibliography. In view of this lack of evidence the committee found merit on the concerns raised by the member states on the potential serious risk to public health.

the CHMP has recommended the refusal of the granting of the marketing authorisation for Loraxin and associated names (see Annex I).

The marketing authorisation for Loraxin and associated names will have to be suspended in the reference Member State, where the product is currently authorised, until such time as adequate data is presented, which will allow a judgment to be made that in spite of the existing formulation differences, Loraxin and the products included in the literature references are considered similar, such that the data generated with these products may be considered relevant to Loraxin, and therefore address the potential serious risk to public health identified by Sweden and Poland.

Annex III

Conditions for the lifting of the marketing authorisation suspension

For the suspension to be lifted the Marketing Authorisation Holder would need to provide the National Competent Authorities with the following:

The Marketing Authorisation Holder is requested to present adequate data, which will allow a judgment to be made that in spite of the existing formulation differences, Loraxin and the products included in the literature references are considered similar, such that the data generated with these products may be considered relevant to Loraxin.