ANNEX I

LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
AU	Aesca chem.pharm. Fabrik GmbH., Badner Straße 23, A-2514 Traiskirchen, Austria	Clarinase - Manteldragees	5 mg loratadine +120 mg pseudoephedrine	Coated tablet	Oral use	Blister	10
AU	Aesca chem.pharm. Fabrik GmbH., Badner Straße 23, A-2514 Traiskirchen, Austria	Clarinase retard Dragees	10 mg loratadine + 240 mg psuedoephedrine	Coated tablet	Oral use	Blister	10
BE	Schering Plough N.V. Rue de Stalle 73 B-1180 Brussels Belgium	Clarinase 120/5 (Repetabs)	5 mg loratadine (+ Pseudo-ephedrine sulfate 120 mg)	Prolonged-release tablet	Oral use	Blister	14 10, 14, 20, 28, 30, 50, 100 – for export
BE	Schering Plough N.V. Rue de Stalle 73 B-1180 Brussels Belgium	Clarinase 240/10 once daily	10 mg loratadine (+ Pseudo-ephedrine sulfate 240 mg)	Prolonged-release tablet	Oral use	Blister	1, 7, 10, 14, 20, 28, 30, 50, 100
BE	Schering Plough N.V. Rue de Stalle 73 B-1180 Brussels Belgium	Prospel	5 mg loratadine (+ Pseudo-ephedrine sulfate 120 mg)	Prolonged-release tablet	Oral use	Blister	10, 14, 4, 10, 20, 28, 30, 50, 100 – for export
FI	Schering-Plough Europe, 73, Rue De Stalle, B-1180 Brussels, Belgium	Clarinase	10 mg loratadine/ 240 mg pseudoeph-edrine	Prolonged-release tablet	Oral use	Blister	1, 7, 10, 14, 20, 28, 30, 50, 100

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
FR	Schering Plough 92, rue Baudin F-92307 Levallois Perret Cedex, France	CLARINASE	10 mg loratadine + 240 mg pseudo-ephedrine sulphate	Prolonged-release tablet	Oral use	Blister (PVC/Alu)	1, 7, 10, 14, 20, 28, 30, 50, 100
FR	Schering Plough 92, rue Baudin F-92307 Levallois Perret Cedex, France	CLARINASE REPETABS	5 mg loratadine + 120 mg pseudoephedrine	Modified-release tablet	Oral use	Blister (PVC/Alu)	10, 14, 20
FR	Schering Plough 92, rue Baudin F-92307 Levallois Perret Cedex, France	LORATADINE/SULFATE de PSEUDOEPHEDRINE	5 mg loratadine + 120 mg pseudoephedrine	Modified-release tablet	Oral use	Blister (PVC/Alu)	10, 14, 20
GR	Schering Plough A.Φ.B.E.E. 63 Agiou Dimitriou GR-17456 Alimos Greece	Clarityne D	5 + 120 mg pseudoe-phine phri-nesulphate	Modified-release tablet	Oral use	Blister	14
GR	Schering Plough A.Φ.B.E.E. 63 Agiou Dimitriou GR-17456 Alimos Greece	Clarityne-D	10 + 240 mg pseudo-epinephrine sulphate	Prolonged-release tablet	Oral use	Blister	7, 14
IC	Schering-Plough Europe, Rue de Stalle, B-1180 Brussels Belgium	Clarinase	10 mg loratadine + 240 mg pseudoephedrine	Prolonged-release tablet	Oral use	Blister	10

IT	Italfarmaco SPA Via Dei Lavoratori, 54 I-20092 Cinisello Balsamo Milano Italy	Frinase	Loratadine 5 mg/pseudoephedrine sulph 120 mg	Modified-release coated tablet	Oral use	Blister	20
IT	Schering Plough SPA Via Ripamonti, 89 I-20141 Milano, Italy	Clarinase	Loratadine 5 mg/pseudoephedrine sulph 120 mg	Modified-release coated tablet	Oral use	Blister	20
IT	Schering Plough SPA Via Ripamonti, 89 I-20141 Milano, Italy	Narinex	Loratadine 10 mg/pseudoephedrine sulph 240 mg	Prolonged-release tablet	Oral use	Blister (ACLAR/PE/PVC)	100
IT	Schering Plough SPA Via Ripamonti, 89 I-20141 Milano, Italy	Narinex	Loratadine 10 mg/pseudoephedrine sulph 240 mg	Prolonged-release tablet	Oral use	Blister (ACLAR/PE/PVC)	1, 7, 10, 14, 20, 28, 30, 50
LU	SCHERING-PLOUGH s.a. 73, Rue de Stalle B-1180 Brussels Belgium	Clarinase 120/5	5 mg + 120 mg pseudoephedrine	Prolonged-release tablet	Oral use	Blister	14
LU	SCHERING-PLOUGH s.a. 73, Rue de Stalle B-1180 Brussels, Belgium	Clarinase 240/10 once daily	10 mg + 240 mg pseudoephedrine	Prolonged-release tablet	Oral use	Blister	7, 10, 20
PT	Schering-Plough Farma, Lda. Rua Agualva dos Açores 16 P-2735-557 Agualva- Cacém Portugal	Claridon	5 mg loratadine + 120 mg pseudo-ephedrine	Modified-release tablet	Oral use	Blister	14, 20
PT	Schering-Plough Farma, Lda. Rua Agualva dos Açores 16 P-2735-557 Agualva- Cacém Portugal	Claridon QD	10 mg loratadine + 240 mg pseudo-ephedrine	Prolonged-release tablet	Oral use	Blister	7, 14

SP	Laboratorios Lesvi S.A. C/Argent 1. Pol. Ind. Can Pelegri ES-08755 Castellbisbal, Barcelona, Spain	Rinociveran	Loratadine10 mg/ pseudoephedrine sulphate 240 mg	Prolonged-release tablet	Oral use	Blister (PVC/AL)	10
SP	Schering-Plough S.A. Km 36 Carret Nacional 1 ES-28750 San Agustin de Guadalix Madrid, Spain	Narine Repetabs	Loratadina 5 mg/pseudoephedrine sulphate 120 mg	Modified-release tablet	Oral use	Blister	20
SP	Schering-Plough S.A. Km 36 Carret Nacional 1 ES-28750 San Agustin de Guadalix Madrid, Spain	Narine Retard	Loratadina 10 mg/ pseudoephedrine 240 mg	Prolonged-release tablet	Oral use	Blister	10

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LORATADINE AND PSEUDOEPHEDRINE CONTAINING MEDICINAL PRODUCTS (see Annex I)

Loratadine is an anti-histamine compound belonging to the H-1 antagonist group and has been on the market of many Member States for at least 10 years. Pseudo-ephedrine is a nasal decongestant, which exerts its sympathomimetic effects indirectly, predominantly through release of adrenergic mediators from postganglionic nerve terminals. The combination of loratadine and pseudoephedrine is on the market as a 5 mg loratadine/120 mg pseudoephedrine or 10 mg loratadine/240 mg pseudoephedrine combination.

In early 1999, the Medical Products Agency (MPA) was made aware of data from the Swedish Medical Birth Registry (SMBR), which indicated that use of loratadine in the first trimester of pregnancy might be associated with an increased risk of hypospadias in the male newborn. The database consisted of 1,020 infants born to women who reported use of loratadine before the first antenatal visit. Further assessment from a preclinical point of view and of the clinical cases resulted in the conclusion that this may have been a random finding. Furthermore, data from a preclinical study did not indicate that loratadine has an anti-androgenic effect, which could be one possible mechanism.

In an analysis from November 2001, the previous signal appeared reinforced. Among 2,780 exposed pregnancies there were in total 15 cases of hypospadias vs. the expected incidence of 6-7 cases. Based on these data, the MPA considered that it could not be excluded that the use of loratadine during the first trimester of pregnancy may be associated with an increased risk of hypospadia.

On 25 April 2002, Sweden triggered a referral to the EMEA under Article 31 of Directive 2001/83/EC, as amended. Based on the data from the Swedish Medical Birth Registry, which could not exclude that the use of loratadine during the first trimester of pregnancy may be associated with increased risk of hypospadia, Sweden considered that there was Community interest in reassessing the full benefit/risk profile of loratadine and requested the CPMP to give an opinion on whether the applications and marketing authorisations for loratadine containing medicinal products should be granted, maintained, changed, suspended or withdrawn.

EFFICACY

A discussion on the efficacy of loratadine containing medicinal products took place in CPMP based on the Rapporteur and Co-Rapporteur's Assessment Reports and the data presented by the Applicants/MAHs.

The CPMP considered that loratadine has been shown to significantly reduce the symptoms of seasonal allergic rhinitis (SAR) when accompanied by nasal congestion. The efficacy was evaluated on the basis of reduction in total rhinitis symptoms and the symptoms of nasal stuffiness. The combination of loratadine and pseudoephedrine was more effective than loratadine alone in improving nasal stuffiness, more effective than pseudoephedrine alone in reducing total symptom scores and significantly more effective than placebo in reducing SAR symptom scores.

The CPMP queried the indication Perennial Allergic Rhinits (PAR). Although the pathophysiology may be the same as for SAR, patients suffering from PAR suffer the whole year, which implies a more chronic use of the combination of loratadine and pseudoephedrine. Furthermore, there is no data available on length of time between treatment courses necessary to assure that recurrence of therapy is driven by congestive symptoms and not related to any dependency phenomena. Following the CPMP's questions relating to appropriate use of combination product in the light of the safety profile of pseudoephedrine the Applicants/MAHs no longer included the indication perennial allergic rhinitis in their proposed Summary of Product Characteristics (SPC) submitted as part of their answers.

The CPMP questioned the use of the combination of loratadine and pseudoephedrine in children below the age of 15 years. Children between the age of 12 and 15 years had been included in the clinical trials evaluating the safety and efficacy of the combination. However, as the efficacy and safey of children below the age of 12 has not been studied a sentence to this effect should be given in section 4.2 of the SPC.

On the basis of the available data the CPMP concluded that the combination of loratadine and pseudoephedrine is effective in the symptomatic treatment of seasonal allergic rhinitis when accompanied by nasal congestion.

SAFETY

The overall safety profile of loratadine containing medicinal products was reviewed by the CPMP. A discussion on the safety of loratadine containing medicinal products took place in CPMP based on the Rapporteur and Co-Rapporteur's Assessment Reports and the data presented by the Applicants/MAHs.

General safety

The CPMP reviewed the available data, which included overall summaries of clinical studies and post-marketing data.

The most frequent adverse reactions reported for loratadine in excess of placebo were somnolence, headache, increased appetite and insomnia. Other adverse reactions reported very rarely during the post-marketing period were: anaphylaxis, dizziness, tachycardia, palpitation, nausea, dry mouth, gastritis, abnormal hepatic function, rash, alopecia, and fatigue. For the loratadine and pseudoephedrine combination products the adverse event profile is comparable to that of loratadine alone except for adverse events like insomnia, dry mouth, dizziness and nervousness, which are commonly or very commonly reported and are likely due to the pseudoephedrine component.

The CPMP queried the safe use of the combination for more than 5 days. The clinical trials were conducted over 14 days and the overall incidence of related AEs reported during the first 5 days was appreciably higher than those reported after 5 days. The CPMP concluded that a statement stating that the duration of treatment should be kept as short as possible and should not be continued after the symptoms have disappeared, should be given in section 4.2 of the SPC. It should also be stated that it is advisable to limit treatment to about 10 days, as the activity of pseudoephedrine diminishes over time.

The benefit/risk of the systemic treatment with the combination of loratadine and pseudoephedrine versus treatment with loratadine and a topical application of pseudoephedrine was discussed. The CPMP considered that topical application of pseudoephedrine is also associated with adverse events, such as tachyphylaxis, rebound congestion, and rhinitis medicamentosa, which may limit the use of topical products.

The CPMP questioned the risk of convulsions induced by vasoconstrictors. A warning was included in section 4.4 with a cross reference to section 4.9 stating that central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines and that these effects may be more likely to occur in children, the elderly, or in cases of overdose.

The CPMP addressed the concerns regarding the safe and appropriate use of the combination of loratadine and pseudoephedrine in the light of the known pharmacodynamic effect of pseudoephedrine on the heart, and the concern for pseudoephedrine related to dependency and addiction. Data to substantiate these concerns were lacking in normal condition of use, in the context of what is required in Article 116 of Directive 2001/83/EC, as amended and CPMP agreed to introduce adequate warnings and precautions in the SPC, this included limiting the indication to seasonal rhinitis to reduce the duration of treatment.

Hypospadias

Studies Conducted to Date

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

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

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

The CPMP considered that possible biases that have been identified in the SMBR, including misclassifications, would bias the risk estimate towards 1 or not affect it. The existence of misclassifications should be viewed as contributing to the strength of the signal. That the effect of non-differential misclassification bias is to underestimate the real association is in line with known epidemiological theory and experience. That there would be any bias in the opposite direction e.g. through the recording of the drug use (the outcome of the pregnancy is not known at the time of the antenatal visit) or the diagnosis of hypospadias is unlikely. The CPMP found that the known confounding factors have been corrected for in the analyses (e.g. parity, smoking, age etc).

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

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

Outcome of pregnancies in women taking loratadine

The CPMP considered the spontaneous post-marketing reports of loratadine use during pregnancy. Approximately 250 cases of loratadine use during pregnancy have been reported. These reports include the 15 hypospadias cases from the SMBR, and 8 spontaneous reports that were received following the initiation of the Article 31 referral procedure. Based on these reports and taking the estimated worldwide use of loratadine into account, the CPMP concluded that the spontaneous reporting data did not raise concerns regarding the use of loratadine during pregnancy. On the other hand, considering an expected considerable underreporting, these data are not robust enough to conclude that use of loratadine during pregnancy is safe.

The total number of loratadine-exposed pregnancies worldwide is unknown, but is probably large. If spontaneous reporting would provide reliable data, a number of hypospadias would have been expected based on the 'natural' background incidence. Hence, the data presented show that hypospadias have not been spontaneously reported as an adverse drug reaction. Thus, the spontaneous reporting provides minor reassurance regarding the safety of loratadine use in pregnancy.

The information available in the medical literature does not indicate an increased risk of congenital malformation with loratadine use. Neither reports of hypospadias nor reports of congenital malformations associated with loratadine were identified in a search of the published literature. Three studies comparing the outcomes of loratadine-exposed pregnancies to controls were identified. In general, the numbers of loratadine-exposed subjects were small (47 to 93 subjects), the study designs varied (prospective vs. retrospective), and the study details were limited.

The CPMP concluded that the three cited studies do not indicate an increased risk of congenital malformations with loratadine use. However, the total number of women exposed to loratadine in these studies is less than 200.

Preclinical studies

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

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

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

OVERALL CONCLUSION ON BENEFIT/RISK

The CPMP concluded that, the available data for loratadine does not indicate that the compound has either genotoxic or antiandrogenic potential.

The CPMP concluded that the SMBR provides a robust signal that loratadine exposure during pregnancy increases the risk of hypospadia. Reasonable biases that have been identified in the SMBR, including misclassifications, cannot explain the occurrence of the signal. The preclinical data argue against a true drug effect. Thus, based on the available data, a causal relationship can neither be confirmed nor excluded. As a precautionary measure the CPMP recommended, that the SPC for loratadine containing medicinal products should be amended to state that the use of loratadine during pregnancy is not recommended. Because pseudoephedrine decreases maternal uterine blood flow the use of the combination of loratadine and pseudoephedrine is contraindicated during pregnancy.

The CPMP concluded that the signal should be further investigated.

The CPMP addressed the concerns regarding the safe and appropriate use of the combination of loratadine and pseudoephedrine in the light of the known pharmacodynamic effect of pseudoephedrine on the heart, and the concern for pseudoephedrine related to dependency and addiction. Data to substantiate these concerns were lacking in normal condition of use, in the context of what is required in Article 116 of Directive 2001/83/EC, as amended and CPMP agreed to introduce adequate warnings and precautions in the SPC, this included limiting the indication to seasonal rhinitis to reduce the duration of treatment.

The Committee considered that the combination of loratadine and pseudoephedrine containing medicinal products are effective in the relief of symptoms associated with seasonal allergic rhinitis accompanied with nasal congestion.

Therefore the CPMP considered that the benefit/risk balance of the combination of loratadine and pseudoephedrine containing medicinal products remains unchanged for the indication "symptomatic treatment of seasonal allergic rhinitis when accompanied by nasal congestion" and recommended the maintenance of the Marketing Authorisations according to the Summary of Product Characteristics as set out in Annex III of the CPMP Opinion with emphasis to the following:

Section 4.6. Pregnancy and lactation

"*Loratadine was not teratogenic in animal studies. The safe use of {INVENTED NAME} during pregnancy has not been established. The use of pseudoephedrine decreases maternal uterine blood flow. The use of {INVENTED NAME} is contraindicated during pregnancy."*

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for loratadine containing medicinal products;
- The Committee concluded that the SMBR provides a robust signal that loratadine exposure during pregnancy increases the risk of hypospadia. Based on the available data, a causal relationship can neither be confirmed nor excluded. As a precautionary measure the CPMP recommended, that the SPC for loratadine containing medicinal products should be amended to state that the use of loratadine during pregnancy is not recommended; furthermore the Committee concluded that because pseudoephedrine decreases maternal uterine blood flow the use of the combination of loratadine and pseudoephedrine is contraindicated during pregnancy;
- The Committee concluded that the signal should be further investigated;
- The CPMP addressed the concerns regarding the safe and appropriate use of the combination of loratadine and pseudoephedrine in the light of the known pharmacodynamic effect of pseudoephedrine on the heart, and the concern for pseudoephedrine related to dependency and addiction. Data to substantiate these concerns were lacking in normal condition of use, in the context of what is required in Article 116 of Directive 2001/83/EC, as amended and CPMP agreed to introduce adequate warnings and precautions in the SPC, this included limiting the indication to seasonal rhinitis to reduce the duration of treatment.
- The Committee considered that the combination of loratadine and pseudoephedrine containing medicinal products are effective in the relief of symptoms associated with seasonal allergic rhinitis accompanied with nasal congestion.
- The Committee, as a consequence considered that the benefit/risk balance of the combination of loratadine and pseudoephedrine containing medicinal products remains unchanged in the relief of symptoms associated with Seasonal Allergic Rhinitis accompanied by nasal congestion.

As a consequence, the CPMP recommended the maintenance of the Marketing Authorisations for the combination of loratadine and pseudoephedrine containing medicinal products referred in Annex I as amended in accordance with the SPC set out in Annex III.

ANNEX III

Note: This SPC is the one that was annexed to the Commission Decision on this Article 31 referral for loratadine and pseudoephedrine containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

{INVENTED NAME} 5 mg/120 mg {pharmaceutical form}
{INVENTED NAME} 10 mg/240 mg {pharmaceutical form}

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Each {pharmaceutical form} contains 5 mg loratadine and 120 mg pseudoephedrine sulphate>
<Each {pharmaceutical form} contains 10 mg loratadine and 240 mg pseudoephedrine sulphate>

[See Annex I - To be completed nationally]

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

<Coated tablet>
<Modified-release tablet>
<Prolonged-release tablet>

<Visual description of the appearance of the product>

[See Annex I - To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{INVENTED NAME} {pharmaceutical form} is indicated for the symptomatic treatment of seasonal allergic rhinitis when accompanied by nasal congestion.

4.2 Posology and method of administration

Adults and children 12 years of age and over:
<[For products containing 10 mg/240 mg]
One *{INVENTED NAME}* {pharmaceutical form} once daily with a glass of water. The {pharmaceutical form} must be swallowed entirely (without crushing, breaking or chewing it). The {pharmaceutical form} may be taken without regard to mealtime.>

<[For products containing 5 mg/120 mg]
One *{INVENTED NAME}* {pharmaceutical form} twice daily with a glass of water. The {pharmaceutical form} must be swallowed entirely (without crushing, breaking or chewing it). The {pharmaceutical form} may be taken without regard to mealtime.>

Not to be administered to children under the age of 12 years, as the safety and efficacy in this population has not been established yet.

The duration of treatment should be kept as short as possible and should not be continued after the symptoms have disappeared. It is advisable to limit treatment to about 10 days, as during chronic administration the activity of pseudo-ephedrine diminishes with time. After improvement of the congestive condition of the mucosae of the upper airway, treatment may be maintained with an antihistamine alone, if necessary.

The combination product should not be administered to patients above 60 years of age or patients with impaired renal or hepatic function (see section 4.4).

4.3 Contraindications

{INVENTED NAME} {pharmaceutical form} is contraindicated in patients who have shown hypersensitivity or idiosyncrasy to either of its components, to any of the excipients or to adrenergic agents.

As *{INVENTED NAME}* contains pseudo-ephedrine it is also contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitor therapy or during the 2 weeks following the stopping of such treatment, and in patients with:

- narrow-angle glaucoma,
- urinary retention,
- cardiovascular diseases such as ischaemic heart disease, tachyarrhythmia and severe hypertension
- hyperthyroidism
- a history of haemorhagic stroke or with risk factors which could increase the risk of haemorhagic stroke, due to the alpha-mimetic activity of the vasoconstrictor, in combination with vasoconstrictors such as bromocriptine, pergolide, lisuride, cabergoline, ergotamine, dihydroergotamine or any other decongestant drug used as nasal decongestant, either by oral route or by nasal route (phenylpropanolamine, phenylephrine, ephedrine…).

<[To be included/deleted nationally as appropriate]
Patients who have had difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal oesophageal peristalsis must not use this product.>

{INVENTED NAME} {pharmaceutical form} must not be used during pregnancy (see section 4.6).

4.4 Special warnings and special precautions for use

Do not exceed the recommended dosage and the duration of treatment (see 4.2).

Patients of 60 years or older are more likely to experience adverse reactions to sympathomimetic medications. The safety and efficacy of the combination have not been established in this population, and there are insufficient data to give adequate dose recommendations. The combination product should not be used in patients above 60 years of age.

Renal or hepatic impairment: The safety and efficacy of the combination have not been established in patients with impaired renal or hepatic function, and there are insufficient data to give adequate dose recommendations. The combination product should not be used in patients with impaired renal or hepatic function.

Patients should be informed that the treatment should be discontinued in case of hypertension, tachycardia, palpitations or cardiac arrhythmias, nausea or any other neurologic sign (such as headache or increased headache).

Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines. These effects may be more likely to occur in children, the elderly, or in cases of overdose (see Section 4.9).

Caution should be exercised in patients receiving digitalis, those with cardiac arrhythmias, hypertension, a history of myocardial infarction, diabetes mellitus, bladder neck obstruction, or positive anamnesis of bronchospasm.

Use with caution in patients with glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, hypertrophy of the prostate, obstruction of the vesical cervix, cardiovascular disease, and increased intra-ocular pressure.

Caution should also be exercised in patients being treated with other sympathomimetics, including decongestants, anorexogenics or amphetamine-type psychostimulants, antihypertensive agents, tricyclic antidepressants and other antihistamines.

Caution should be exercised in patients suffering from migraine treated with ergot alkaloid vasoconstrictors.

As with other CNS stimulants, pseudo-ephedrine sulphate carries the risk of abuse. Increased doses may ultimately produce toxicity. Continuous use can lead to tolerance resulting in an increased risk of overdosing. Depression may follow rapid withdrawal.

Perioperative acute hypertension can occur if volatile halogenated anaesthetics are used during treatment with indirect sympathomimetic agents. Therefore, if surgery is scheduled, it is preferable to discontinue treatment 24 hours before anaesthesia.

Athletes should be informed that treatment with pseudoephedrine could lead to positive dope-tests.

The administration of *{INVENTED NAME}* should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.

4.5 Interaction with other medicinal products and other forms of interaction

When administered concomitantly with alcohol loratadine has no potentiating effects as measured by psychomotor performance studies.

Due to the wide therapeutic index of loratadine no clinically relevant interactions are expected and none were observed in the conducted clinical trials (see 5.2).

Concurrent administration of monoamine oxidase inhibitors and sympathomimetic drugs can cause critical hypertension reactions.

Sympathomimetic drugs reduce the antihypertensive effect of α-methyldopa, mecamylamine, reserpine, veratrum alkaloids, and guanethidine.

The following combinations are not recommended:
Bromocriptine, cabergoline, lisuride, pergolide : risk of vasoconstriction and increase in blood pressure.

Dihydroergotamine, ergotamine, methylergometrine (dopaminergic vasoconstricteurs) : risk of vasoconstriction and increase in blood pressure.

Linezolide : risk of vasoconstriction and increase in blood pressure.

Other vasoconstrictors used as nasal decongestant, by oral or nasal route, (phenylpropanolamine, phenylephrine, ephedrine…): risk of vasoconstriction.

Antacids increase the rate of pseudoephedrine sulphate absorption, kaolin decreases it.

4.6 Pregnancy and lactation

Loratadine was not teratogenic in animal studies. The safe use of {INVENTED NAME} during pregnancy has not been established. The use of pseudoephedrine decreases maternal uterine blood flow. The use of {INVENTED NAME} is contraindicated during pregnancy.

{INVENTED NAME} is excreted is breast milk, therefore the use of *{INVENTED NAME}* is not recommended in breast-feeding women.

4.7 Effects on ability to drive and use machines

In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, some people very rarely experience drowsiness, which may affect their ability to drive or use machines.

It is not expected that pseudoephedrine sulphate impairs psychomotor performance.

4.8 Undesirable effects

<[For products containing 10 mg/240 mg]

Adverse reactions reported during clinical trials in excess of placebo for 10 mg/240 mg {Pharmaceutical form} very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000)	
Psychiatric disorders Common:	Anorexia, nervousness, somnolence, insomnia
Nervous system disorders (Peripheral and Central) Common:	Dizziness, hyperkenesia
Autonomic Nervous system disorders Common:	Dry mouth
Cardiac disorders Uncommon:	Tachycardia, palpitation
Respiratory, thoracic and mediastinal disorders Uncommon:	Rhinitis, epistaxis
Gastrointestinal disorders Uncommon:	Constipation, nausea
Body as a whole-General disorders Common:	Fatigue

<[For products containing 5 mg/120 mg]

Adverse reactions reported during clinical trials in excess of placebo for 5 mg/120 mg {Pharmaceutical form} very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000)	
Metabolic and Nutrition Disorders Common:	 Thirst
Psychiatric disorders Common: Very Common:	 Nervousness, somnolence, depression, agitation, anorexia Insomnia
Nervous system disorders (Peripheral and Central) Uncommon: Common:	 Confusion, tremor Dizziness
Autonomic Nervous System Disorders Uncommon: Very Common:	 Increased sweating, hot flushes, taste perversion Dry mouth
Eye Disorders Uncommon:	 Abnormal lacrimation
Ear and Labyrinth Disorders Uncommon:	 Tinnitus
Cardiac disorders Uncommon: Common:	 Palpitation Tachycardia
Respiratory, thoracic and mediastinal disorders Uncommon: Common:	 Epistaxis Pharyngitis, rhinitis
Gastrointestinal disorders Common:	 Constipation, nausea
Renal and urinary disorders Uncommon:	 Micturition frequency and disorder
Skin and subcutaneous tissue disorders Uncommon	 Pruritus
Body As a Whole – General Disorders Common:	 Headache, fatigue

>

Other adverse reactions reported very rarely during the post-marketing period are listed in the following table.

Immune disorders	Anaphylaxis
Nervous system disorders	Vertigo
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Cough, bronchospasm
Hepato-biliary disorders	Abnormal hepatic function
Renal and urinary disorders	Urinary retention
Skin and subcutaneous tissue disorders	Alopecia

Other adverse reactions that were only reported for loratadine in clinical trials and during the post marketing period include increased appetite, rash and gastritis.

4.9 Overdose

Symptoms of overdose are mostly of a sympathomimetic nature, except for slight sedation that can be caused by loratadine at doses many times higher than the recommended dose. Symptoms may vary from CNS depression (sedation, apnoea, diminished mental alertness, cyanosis, coma, cardiovascular collapse) to CNS stimulation (insomnia, hallucination, tremors, convulsions) with possible fatal outcome. Other symptoms may include: headache, anxiety, micturition difficulty, muscle weakness and tenseness, euphoria, excitement, tachycardia, palpitations, thirst, perspiration, nausea, vomiting, precordial pain, dizziness, tinnitus, ataxia, blurred vision and hypertension or hypotension. CNS stimulation is particularly likely in children, as are atropine-like symptoms (dry mouth, fixed and dilated pupils, flushing, hyperthermia, and gastrointestinal symptoms).

Treatment: In the event of overdosage, start symptomatic and supportive treatment immediately and maintain it for as long as necessary. Adsorption of active substance remaining in the stomach may be attempted by administration of active charcoal suspended in water. Perform gastric lavage with physiologic saline solution, particularly in children. In adults, tap water can be used. Remove as much as possible of the amount administered before the next instillation. Loratadine is not removed by haemodialysis and it is not known if loratadine is eliminated by peritoneal dialysis. After emergency treatment, continue to monitor the patient medically.

Treatment of the pseudoephedrine overdosage is symptomatic and supportive. Stimulants (analeptics) must not be used. Hypertension can be controlled with an alpha-blocking agent and tachycardia with a beta-blocking agent. Short acting barbituates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or hypothermia blanket. Apnoea is treated with respiratory assistance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines – H_1 antagonist, ATC code: R06A X13.
Pharmacotherapeutic group: Nasal decongestants for systemic use group, ATC code: R01BA52.

The pharmacodynamics of *{INVENTED NAME}* tablets are directly related to that of its components.

Loratadine is a tricyclic antihistamine with selective, peripheral H_1-receptor activity. Loratadine has no significant H_2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.

During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.

Pseudoephedrine sulfate (d-isoephedrine sulfate) is a sympathomimetic agent with mostly α-mimetic activity in comparison with the β-activity. Pseudoephedrine sulfate 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.

Oral administration of pseudoephedrine at the recommended dose can cause other sympathomimetic effects, such as increased blood pressure, tachycardia or manifestations of central nervous system excitation.

5.2 Pharmacokinetic properties

Loratadine: After oral administration, loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desloratadine (DL) is pharmacologically active and responsible for a large part of the clinical effect. Loratadine and DL achieve maximum plasma concentrations (T_{max}) between 1–1.5 hours and 1.5–3.7 hours after administration, respectively.

Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).

Loratadine is highly bound (97 % to 99 %) and its active metabolite moderately bound (73 % to 76 %) to plasma proteins.

In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively. The mean elimination half-lives are 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the active metabolite.

Approximately 40 % of the dose is excreted in the urine and 42 % in the faeces over a 10 day period and that, mainly in the form of conjugated metabolites. Approximately 27 % of the dose is eliminated in the urine during the first 24 hours. Less than 1% of the active substance is excreted unchanged in active form, as loratadine or DCL.

The bioavailability of loratadine and of the active metabolite is proportional to the administered dose.

The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

In patients with chronic renal impairment, both the AUC and peak plasma levels (C_{max}) increased for loratadine and its metabolite as compared to the AUCs and peak plasma levels (C_{max}) of patients with normal renal function. The mean elimination half-lives of loratadine and its metabolite were not significantly different from those observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.

In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (C_{max}) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and its metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Loratadine and its active metabolite are excreted in the breast milk of lactating women.

Pseudoephedrine sulfate: After oral administration, pseudoephedrine sulfate is rapidly and completely absorbed. Onset of action occurs within 30 minutes and a dose of 60 mg has a decongestive action lasting for 4 to 6 hours. Pseudoephedrine sulfate undergoes incomplete hepatic metabolism by N-demethylation to an inactive metabolite.

Its elimination half-life in humans, at an approximate urinary pH of 6, ranges from 5 to 8 hours. The active substance and its metabolite are excreted in urine, 55-75 % of the administered dose is excreted unchanged. The rate of excretion is accelerated and the duration of action decreased in acidic urine (pH5). In case of alkalinization of the urine, a partial resorption takes place.

Pseudoephedrine is presumed to cross the placenta and the haematoencephalic barrier.

The active substance is excreted in breast milk of lactating women.

Food may increase the amount of loratadine absorbed, but without clinically significant results. This is not observed with pseudoephedrine.

5.3 Preclinical safety data

Preclinical data for loratadine reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Toxicity for the combination: In acute and multiple-dose studies, the combination of loratadine/pseudoephedrine sulfate exhibited a low order of toxicity. The combination was not more toxic than their individual components, and observed effects were generally related to the pseudoephedrine component.

In reproductive toxicity studies of loratadine, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats at plasma levels (AUC) 10 times higher than those achieved with clinical doses.

During reproductive toxicity studies, the combination of loratadine/pseudoephedrine was not teratogenic when administered orally to rats at doses up to 150 mg/kg/day (30 times the proposed clinical dose) and rabbits at doses up to 120 mg/kg/day (24 times the proposed clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[See Annex I - To be completed nationally]

7. MARKETING AUTHORISATION HOLDERS

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

