Public Assessment Report

Mutual Recognition Procedure

Loratadine 10 mg Tablets

UK/H/0812/01
UK Licence no: PL 14894/0112

Ranbaxy (UK) Limited

TABLE OF CONTENTS

Module 1: Information about initial procedure Page 3

Module 2: Summary of Product Characteristics Page 4

Module 3: Product Information Leaflets Page 10

Module 4: Labelling Page 11

Module 5: Scientific Discussion Page 12

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 1

Product Name	Loratadine 10 mg Tablets
Type of Application	Generic Article 10.1
Active Substance	Loratadine
Form	Tablets
Strength	10mg
MA Holder	Ranbaxy (UK) Limited 95 Park Lane, Mayfair London, W1K 7TE United Kingdom
RMS	United Kingdom
CMS	Austria, Belgium, Denmark, Estonia, Greece, Italy, Latvia, Lithuania, The Netherlands, Norway, Portugal, Poland, Slovak Republic, Spain and Sweden
Procedure Number	UK/H/0812/01
Timetable	D90 - 22nd March 2006

Module 2

Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Loratadine 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg loratadine.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets

White to off-white, round, uncoated tablets debossed with “R” on one side and “10” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Loratadine 10mg Tablets is indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

4.2 Posology and method of administration

Adults and children over 12 years of age: 10mg once daily (one tablet once daily). The tablet may be taken without regard to mealtime.

Children 2 to 12 years of age with:
Body weight more than 30kg: 10mg once daily (one tablet once daily).

The 10mg strength tablet is not appropriate in children with a body weight less than 30kg.

Efficacy and safety of Loratadine 10 mg Tablets in children under 2 years of age has not been established. The use is therefore not recommended in these patients.
Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine. An initial dose of 10mg every other day is recommended for adults and children weighing more than 30kg, and for children weighing 30kg or less, 5mg every other day is recommended.

No dosage adjustments are required in the elderly or in patients with renal

insufficiency.

4.3 Contraindications

Loratadine 10 mg Tablets is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients in these formulations.
In children under 2 years. (see section 4.2)
During pregnancy or lactation (see section 4.6)

4.4 Special warnings and special precautions for use

Loratadine 10 mg Tablets should be administered with caution in patients with severe liver impairment (see Section 4.2).

The administration of Loratadine 10 mg Tablets should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.

These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

There are no significant interactions between loratadine and food.

4.5 Interaction with other medicinal products and other forms of interaction

When administered concomitantly with alcohol, Loratadine 10 mg Tablets 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 Section 5.2).

4.6 Pregnancy and lactation

Loratadine was not teratogenic in animal studies. The safe use of loratadine during pregnancy has not been established. The use of Loratadine 10 mg Tablets during pregnancy is therefore not recommended.
Loratadine is excreted in breast milk, therefore the use of loratadine 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, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.8 Undesirable effects

In clinical trials in a paediatric population children aged 2 through 12 years, common adverse reactions reported in excess of placebo were headache (2.7%), nervousness (2.3%), and fatigue (1%).

In clinical trials involving adults and adolescents in a range of indications including allergic rhinitis and chronic idiopathic urticaria , at the recommended dose of 10mg daily, adverse reactions with loratadine were reported in 2% of patients in excess of those treated with placebo. The most frequent adverse reactions reported in excess of placebo were somnolence (1.2%), headache (0.6%), increased appetite (0.5%) and insomnia (0.1%). Other adverse reactions reported very rarely during the post-marketing period are listed in the following table.

Immune disorders	Anaphylaxis
Nervous system disorders	Dizziness
Cardiac disorders	Tachycardia, palpitation
Gastrointestinal disorders	Nausea, dry mouth, gastritis
Hepato-biliary disorders	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Rash, alopecia
General disorders and administration site conditions	Fatigue

4.9 Overdose

Overdosage with loratadine increased the occurrence of anticholinergic symptoms. Somnolence, tachycardia, and headache have been reported with overdoses.

In the event of overdosage, general symptomatic and supportive measures are to be instituted and maintained for as long as necessary. Administration of activated charcoal as a slurry with water may be attempted. Gastric lavage may be considered. Loratadine is not removed by haemodialysis and it is not known if loratadine is removed by peritoneal dialysis. Medical monitoring of the patient is to be continued after emergency treatment

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines – H_1 antagonist, ATC code: R06A X13.

Loratadine, the active ingredient in Loratadine 10 mg Tablets, is a tricyclic antihistamine with selective, peripheral H_1-receptor 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.
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.

5.2 Pharmacokinetic properties

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 in healthy adult subjects were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite.

Approximately 40% of the dose is excreted in the urine and 42% in the faeces over a 10 day period and 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 DL.

The bioavailability parameters of loratadine and of the active metabolite are dose proportional

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

Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect.

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 that 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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies, 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.

No evidence of mucous membrane irritation was observed after daily administration of up to 12 tablets (120mg) of oral lyophilisates into the hamster cheek pouch for five days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original pack.

6.5 Nature and contents of container

Blister strip comprising of clear transparent PVC film (coated uniformly with PVdC on the inner side) with a backing of aluminium foil (coated with heat seal lacquer). 7, 10, 14, 21, 30, and 100 tablets per pack.

6.6 Instructions for Use/Handling

None

7. MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
95 Park Lane, Mayfair,
London W1K 7TE

8. MARKETING AUTHORISATION NUMBER

14894 / 0112

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19th September 2003

10. DATE OF REVISION OF THE TEXT

Module 3

Product Information Leaflet

PATIENT INFORMATION LEAFLET

Loratadine 10 mg Tablets

(Loratadine)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

1. **What Loratadine Tablets are and what they are used for**
2. **Before you take Loratadine Tablets**
3. **How to take Loratadine Tablets**
4. **Possible side effects**
5. **How to store Loratadine Tablets**
6. **Further information**

1. What Loratadine Tablets are and what they are used for

Loratadine belongs to the class of medicines called anti-histamines, which are used to treat various allergic conditions.
Loratadine tablets are used to relieve symptoms associated with seasonal allergic rhinitis (hay fever) and perennial allergic rhinitis (year round allergy symptoms). Symptoms of these conditions can include sneezing, runny nose, nasal itching, in addition to burning, itching and watering of the eyes.
Loratadine tablets are also used to relieve symptoms of chronic idiopathic urticaria (skin rash consisting of hives and wheals)

2. Before you take Loratadine Tablets

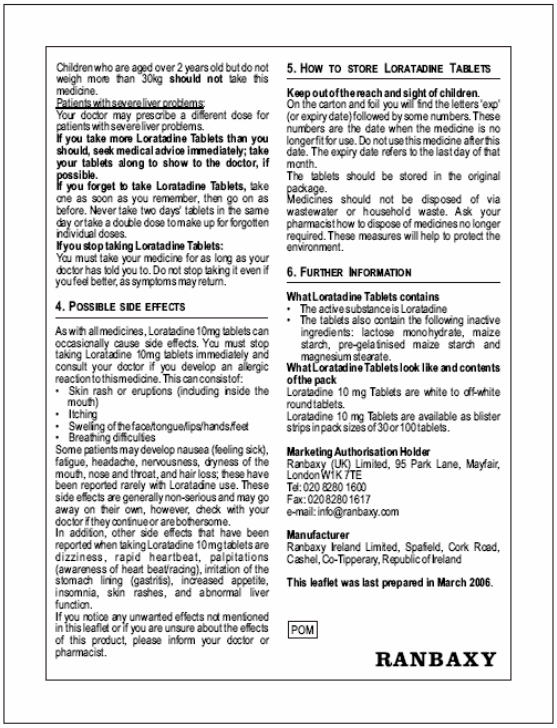
Do not take Loratadine Tablets if:
- you are allergic (hypersensitive) to Loratadine or any of the other ingredients of Loratadine Tablets. An allergic reaction can include skin rash, itching, swelling or breathing difficulties.)
- you are pregnant or planning to become pregnant
- you are breast-feeding currently
- you are a child under two.

Before you start to take the tablets make sure your doctor knows if:
- you have severe liver problems
- you have been told that you have an intolerance to some sugars
- you are due to have skin tests since Loratadine Tablets could affect the results.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.
Driving and using machines:
Very rarely, this medicine may cause drowsiness or reduced alertness in some people. Hence, you should not perform such tasks that need special attention (including driving a car or operating machinery), until you know how this medicine affects you.

3. How to take Loratadine Tablets

Always take Loratadine Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Loratadine is provided as tablets. The tablet should be swallowed whole with a drink of water.
Take your medicine as instructed by your doctor. Check the label carefully for instructions on how much and how often to take. To help you to remember to take your medicine, try to get into the habit of taking it at the same time every day.
Usual Doses
Adults/Children over 12 years old: 10mg once daily (one tablet once daily)
Children aged 2 to 12 *and* weighing over 30kg: 10mg once daily (one tablet once daily)



Children who are aged over 2 years old but do not weigh more than 30kg **should not** take this medicine.
Patients with severe liver problems:
Your doctor may prescribe a different dose for patients with severe liver problems.
If you take more Loratadine Tablets than you should, seek medical advice immediately; take your tablets along to show to the doctor, if possible.
If you forget to take Loratadine Tablets, take one as soon as you remember, then go on as before. Never take two days' tablets in the same day or take a double dose to make up for forgotten individual doses.
If you stop taking Loratadine Tablets:
You must take your medicine for as long as your doctor has told you to. Do not stop taking it even if you feel better, as symptoms may return.

4. Possible side effects

As with all medicines, Loratadine 10mg tablets can occasionally cause side effects. You must stop taking Loratadine 10mg tablets immediately and consult your doctor if you develop an allergic reaction to this medicine. This can consist of:
- Skin rash or eruptions (including inside the mouth)
- Itching
- Swelling of the face/tongue/lips/hands/feet
- Breathing difficulties

Some patients may develop nausea (feeling sick), fatigue, headache, nervousness, dryness of the mouth, nose and throat, and hair loss; these have been reported rarely with Loratadine use. These side effects are generally non-serious and may go away on their own, however, check with your doctor if they continue or are bothersome.
In addition, other side effects that have been reported when taking Loratadine 10mg tablets are dizziness, rapid heartbeat, palpitations (awareness of heart beat/racing), irritation of the stomach lining (gastritis), increased appetite, insomnia, skin rashes, and abnormal liver function.
If you notice any unwanted effects not mentioned in this leaflet or if you are unsure about the effects of this product, please inform your doctor or pharmacist.

5. How to store Loratadine Tablets

Keep out of the reach and sight of children.
On the carton and foil you will find the letters 'exp' (or expiry date) followed by some numbers. These numbers are the date when the medicine is no longer fit for use. Do not use this medicine after this date. The expiry date refers to the last day of that month.
The tablets should be stored in the original package.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Loratadine Tablets contains
- The active substance is Loratadine
- The tablets also contain the following inactive ingredients: lactose monohydrate, maize starch, pre-gelatinised maize starch and magnesium stearate.

What Loratadine Tablets look like and contents of the pack
Loratadine 10 mg Tablets are white to off-white round tablets.
Loratadine 10 mg Tablets are available as blister strips in pack sizes of 30 or 100 tablets.

Marketing Authorisation Holder
Ranbaxy (UK) Limited, 95 Park Lane, Mayfair, London W1K 7TE
Tel: 020 8280 1600
Fax: 020 8280 1617
e-mail: info@ranbaxy.com

Manufacturer
Ranbaxy Ireland Limited, Spafield, Cork Road, Cashel, Co-Tipperary, Republic of Ireland

This leaflet was last prepared in March 2006.

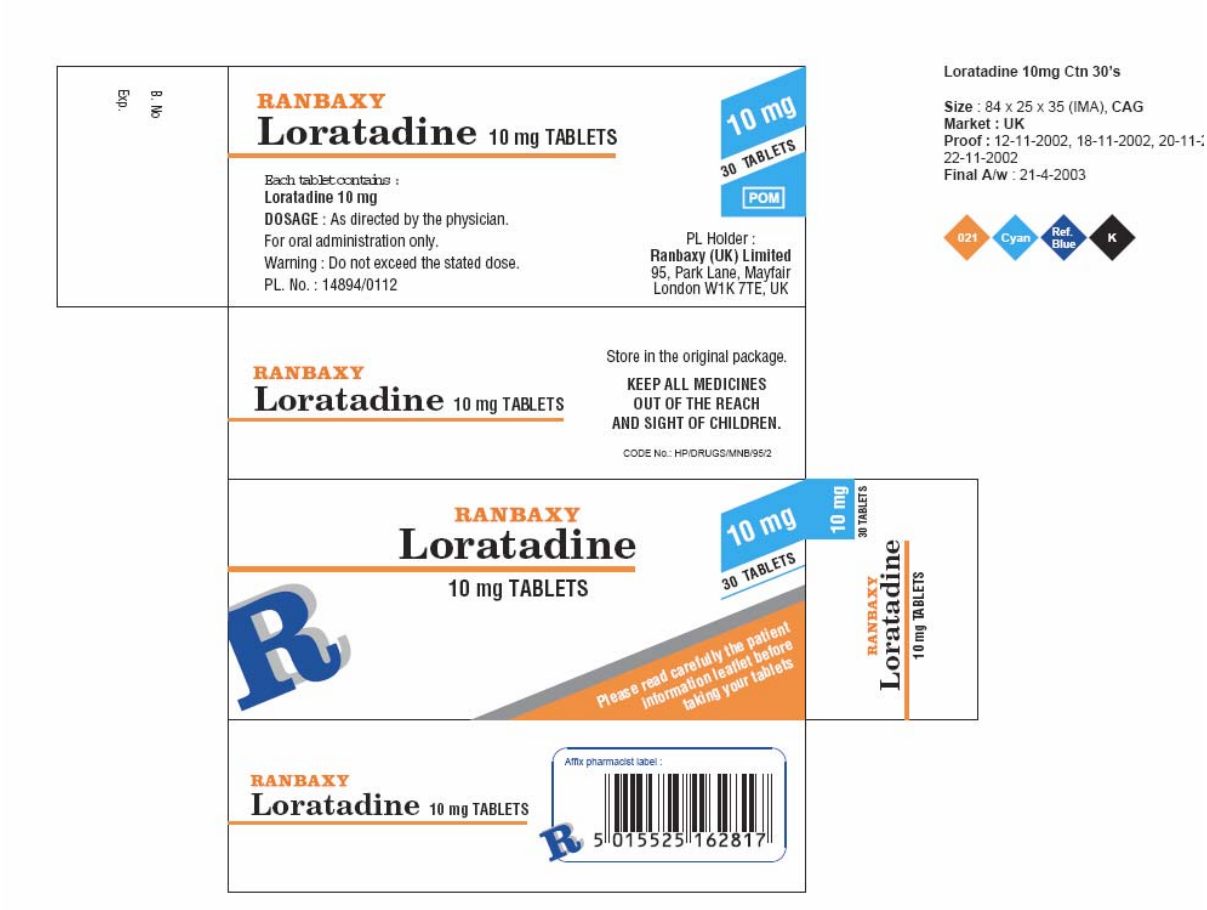
POM

RANBAXY

Loratadine 10 mg Tablets PIL
Insert Size : 130 x 170 mm
Point Size : 8 Pt.
Market : UK
RLL/PKGDEV - 21/03/2006
27/04/2006

Module 4

Labelling



Module 5

Scientific Discussion during Initial Procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Loratadine 10 mg, from Ranbaxy (UK) Ltd. for the the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

This application was made under Article 10.1 [formerly Article 10.1(a)(iii), first paragraph of 2001/83 EC] for generic Loratadine 10 mg Tablets, with reference to Clarityn 10mg Tablets (PL 00201/0175) licensed to Schering-Plough (UK). The brand leader was first approved in the UK on 22nd February1989 and has been in clinical use since.

Loratadine, the active ingredient in Loratadine 10 mg Tablets, is a tricyclic antihistamine with selective, peripheral H1-receptor activity.

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The RMS has been assured that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

This product was granted marketed authorisations on 19th September 2003. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Ranbaxy (UK) Limited.) gained approval for marketing authorisations in Austria (AT), Italy (IT), The Netherlands (NL), Norway (NO), Portugal (PT), Sweden (SE), Belgium (BE), Denmark (DK), Estonia (EE), Latvia (LV), Lithuania (LT), Poland (PL), Slovak Republic (SK), Greece (EL) and Spain (ES).

Loratadine 10 mg Tablets are available on prescription.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Loratadine 10 mg Tablets
Name of the active substance	Loratadine
Pharmacotherapeutic classification (ATC code)	R06A X13
Pharmaceutical form and strength	Tablets, 10 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/812/01
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Denmark, Estonia, Greece, Italy, Latvia, Lithuania, The Netherlands, Norway, Portugal, Poland, Slovak Republic, Spain and Sweden
Name and address of manufacturer responsible for batch release in the EEA	Ranbaxy Ireland Limited Spafield, Cork Road Cashel, Co. Tipperary Republic of Ireland
Date of first authorisation	19th September 2003
Marketing Authorisation Number(s)	PL 14894/0112
Date of assessment report	21st July 2005
Authorisation holder's name and address	Ranbaxy (UK) Limited 95 Park Lane, Mayfair London, W1K 7TE United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

The active substance is loratadine. The starting material is 8-chloro-10,11-dihydro-4-aza-5H-dibenzo-[a,d]-cyclohepten-5-one ('cyclic ketone'), which can be purchased commercially. A detailed evaluation of the process, critical steps, process validation, process development and in-process controls have been assessed and approved

Different polymorphs have been described in the literature of loratadine. It is stated that for this product the active substance synthesised is loratadine polymorphic form 1 (higher melting point). Two forms exist that can be distinguished by IR spectra and DSC thermograms.

The active substance specification is considered acceptable to ensure the quality of loratadine from the synthesis described. The analytical methods used for quality control of loratadine are appropriately described and validated. The retest interval has been justified with data from appropriate stability studies.

P Medicinal Product

P.1 Composition

Composition

Loratadine tablets are white / off-white, round, uncoated tablets, engraved '10' and 'R' on opposite sides. The product is composed of standard pharmacopoeial excipients for manufacture of an uncoated tablet using wet granulation. All excipients are controlled in accordance with Ph Eur. The nominal tablet weight is 100mg.

Container/closure system

The primary container is a blister strip within an outer carton and the pack sizes are 7, 10, 14, 21, 30 and 100 tablets

P.2 Pharmaceutical development

The objective of the development programme has been a globally acceptable, stable and bioequivalent tablet dosage form of loratadine, comparable to Clarityn 10mg Tablets (Schering-Plough (UK)).

A qualitative comparison of the composition of the reference product (UK) and other EU brand leader products has shown the same formula.

The development programme has been well described and includes excipient compatibility, functionality and relevant formulation and process development optimisation studies.

The dissolution method was shown to be discriminatory. Comparative dissolution studies have been carried out with the biobatches, UK brand leader and several EU brands.

The applicant has carried out an impurity profile comparison against the brand leader. The results show that the impurity profile of the applicant's product is comparable to that of the brand leader.

The particle size specification provides reassurance of conformity of the dissolution profile with the batch used in the bioequivalence studies, and is therefore accepted.

Clinical trial formula(e)
The formulation of the batch used in the bioequivalence study is identical to that proposed for marketing.

P.3 Method of preparation of the product
The method of manufacture is conventional. A satisfactory flow chart of the manufacturing process has been provided. The equipment used for pilot batches (including the biobatch) and commercial batches are the same.

In-process control
In-process controls are specified for the precompression blend, tablets sampled during compression and integrity control of the sealed blisters. The controls are acceptable.

Process validation
A process validation protocol has been provided and is considered to be satisfactory given the batch data presented and the conventional nature of the manufacturing procedure and the drug product.

P.4 Control of other substance(s) (excipients)
All excipients comply with the specified Ph Eur monographs. Certificates of Analysis demonstrating compliance with current Ph Eur monographs and in-house specifications have been provided. The finished product manufacturer performs satisfactory tests as appropriate on receipt of the excipients.

Animal tissues are used in the manufacture of Magnesium stearate. A Ph Eur Certificate of Suitability has been provided to demonstrate the suitability of this excipient from this source. This is satisfactory.

Calf rennet may be used in the production process for lactose. Evidence of compliance with Ph Eur TSE requirements has been provided.

P.5 Control tests on the finished product

The specification is comprehensive and contains relevant controls for this type of product and set limits are in line with batch data.

Test methods have been adequately described and validated.
Loratadine working standard was calibrated against the USPRS. No Ph Eur or BP reference substance was available at the time of assessment and the USPRS was therefore acceptable.

P.6 Packaging Materials
Satisfactory specifications and Certificates of Analysis have been provided for packaging materials, which conform to relevant European Directives concerning plastic materials in contact with foodstuffs. The finished product manufacturer performs satisfactory tests, as appropriate, on receipt of the packaging components.

P.7 Stability tests on the finished product
Stability data has been generated for two full scale batches of finished product. Samples have been stored in the proposed commercial packaging for up to 36 months at 25°C/60%RH, and at 40°C/75% RH for 6 months. Analytical methods were the same as those described for product at release.

Studies have also been conducted on bulk packed tablets stored in simulated shipping containers.

A shelf-life of 36 months with the storage direction ‘store in the original package’ is justified by the stability data.

CONCLUSION ON QUALITY

The pharmaceutical assessor concluded that marketing authorisations may be granted for this product.

III.2 PRE-CLINICAL ASPECTS

This application for a generic product claims essential similarity to Clarityn 10 mg Tablets (Schering Plough (UK)), which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with this application, however, a preclinical expert report, summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

III.3 CLINICAL ASPECTS
III.3.1 Clinical Pharmacology

Pharmacokinetics

Introduction and Summary:

The applicant has not submitted any new data on clinical pharmacology of loratadine and none are required as per Article 10.1. A summary of current knowledge on pharmacokinetics of loratadine is provided.

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 (Tmax) between 1-1.5 hours and 1.5-3.7 hours after administration, respectively.

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

Approximately 40% of the dose is excreted in the urine and 42% in the faeces over a 10 day period and 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 DL.

The bioavailability parameters of loratadine and of the active metabolite are dose proportional

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

Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect.

Interactions

When administered concomitantly with alcohol, Loratadine 10 mg Tablets 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

Special Populations

Loratadine 10 mg Tablets should be administered with caution in patients with severe liver impairment (see Section 4.2 of the SPC).

The administration of Loratadine 10 mg Tablets should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.

These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pharmacodynamics

Introduction

Loratadine, the active ingredient in Loratadine 10 mg Tablets, is a tricyclic antihistamine with selective, peripheral H_1-receptor 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.

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.

Bioavailability & Bioequivalence

Bioavailability

The bioavailability of the generic compound was not assessed separately, but as a part of the bioequivalence study that is addressed below:

Bioequivalence Study

In accordance with requirements, the applicant has submitted a bioequivalence study comparing the generic product with the reference product. A summary is provided below. It is stated that the study conformed to GCP guidelines.

BE Study:

Methodology	Randomised, open-label, single-dose cross-over studies: Twenty-six healthy male volunteers were randomised to take each preparation as a singl 10mg oral dose separated by a washout period of 21 days. Fluid and food were appropriatel restricted and medication was taken following an overnight fast with 240ml drinking wate Venous blood samples were taken pre-dose and up to 96 hours following each medicatio Loratadine and the major metabolite descarboethoxyloratidine were measured by LCMS/M with a lower limit of quantification of 0.245ng/ml and 0.251ng/ml for loratadine an descarboethoxyloratidine respectively. 24 subjects were intended for the statistical analysi with dropouts to be replaced to give 24 subjects if necessary.
Subjects	Twenty-four subjects completed the study. There were two drop-outs in the second period – subjects 5 and 11; subject five was withdrawn due to a low predose haemoglobin in Part II; subject 11 developed chicken pox. Only one standby subject number 25 was enrolled and therefore only pharmacokinetic analysis results for 23 were subjects included in the final report signed 31st July 2001. Subject 26's data are not given in any report nor is their omission commented on.

Summary of Pharmacokinetic Data for Parent Loratidine (test) and Clarityn (ref.)

Dose 10mg SD n=23

Variable	**Unit**	**(Reference) Arithmetic Mean SD**	**(Test) Arithmetic Mean SD**	**Intrasubject CV %**	**Ratio of Means %**	**90% Confidence interval (%)****
Cmax	(ng/ml)	7.36	8.42	28.7	97.51	84.5-112.5
AUC	(ng.h/ml)	26.83	23.18	17.3	98.99	90.5-108.3

* Point estimate of "test/reference" mean ratio from analysis of variance of log-transformed data.

** 90% Conventional confidence interval for the "test/reference" mean ratio analysis of variance of log-transformed data.

Summary of Pharmacokinetic Data for Descarboethoxyloratidine metabolite for Loratidine (test) and Clarityn (ref)

Dose 10mg SD n=23

Variable	Unit	(Reference) Arithmetic Mean SD	(Test) Arithmetic Mean SD	Intrasubject CV %	Ratio of Means %	90% Confidence interval (%)**
Cmax	(ng/ml)	4.64	4.92	21.1	104.57	94.1-116.2
AUC	(ng.h/ml)	45.27	49.14	15.1	107.42	99.5-115.9

* Point estimate of "test/reference" mean ratio from analysis of variance of log-transformed data.

** 90% Conventional confidence interval for the "test/reference" mean ratio analysis of variance of log-transformed data.

The data suggest that the two products under test are bioequivalent. If this can be established, since the comparator licence was granted more than ten years ago and has been continually marketed since that time within the EU, and is marketed in the UK, the applicant can claim essential similarity for the same indications as the originator.

III.3.2 Clinical Efficacy

No new efficacy data were submitted by the applicant. The applicant has provided sufficient bibliographic data to support the conclusions. The documented clinical efficacy of the active remains satisfactory for the claimed indications and the proposed dosages.

III.3.3 Clinical Safety

No new safety data were submitted with the application. The recorded safety profile of the active remains satisfactory when used in the claimed indications and at the recommended dosages. Safety findings in the bioequivalence study were those associated with the drug's use - and were similar and of comparable intensity between the two products.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This is a generic application based on essential similarity to an established active (brand leader) that was authorised in 1989. The applicant has not submitted any pharmacological data except for bioequivalence. This is acceptable.

It is accepted that bioequivalence has been demonstrated with the reference product.

No new efficacy or safety data have been included in the dossier and none are necessary for an application based on essential similarity.

It is accepted that risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SPC includes all relevant warnings.

There are no pre-clinical concerns with these applications or with the clinical use of loratadine.