Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Levocetirizine dihydrochloride 5 mg film-coated Tablets

(Levocetirizine dihydrochloride)

UK/H/1416/01/DC
UK/H/1417/01/DC
UK/H/1418/01/DC
UK/H/1434/01/DC
UK/H/1435/01/DC
UK/H/2331/01/DC
UK/H/1420/01/DC
UK/H/3086/01/DC

Applicant:

Synthon BV

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency (MHRA) granted Synthon BV Marketing Authorisations (licences) for the medicinal product Levocetirizine Dihydrochloride 5 mg film-coated tablets. This medicine is available on prescription only.

Oral anti-histamines, such as cetirizine and levocetirizine, are considered first-line treatment for allergic conditions, such as hay fever; year round allergies such as dust or pet allergies and chronic nettle rash.

Cetirizine is a racemate (mixture of equal amounts of enantiomers), comprised of an R- and S-enantiomers (molecules that are mirror-images of one-another). Levocetirizine is the R-enantiomer of the racemate cetirizine.

Levocetirizine is anti-histamine, which means that it blocks the action of histamine, a natural substance found in the body that can cause the symptoms of some allergies.

Bioequivalence has been demonstrated for the active R-enantiomer between this generic levocetirizine and the reference product Zyrtec ® (UCB Pharma). No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Levocetirizine Dihydrochloride 5 mg film-coated tablets outweigh the risks; hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Levocetirizine dihydrochloride 5 mg film-coated Tablets
Type of Application	Generic, Article 10.3
Active Substance	Levocetirizine dihydrochloride
Form	Film-coated tablets
Strength	5mg
MA Holder	Synthon BV Microweg 22 6545 CM Nijmegen The Netherlands
RMS	UK
CMS	UK/H/1416/001/DC - Germany, France, Italy, Luxembourg, The Netherlands UK/H/1417/001/DC - Germany UK/H/1418/001/DC - Germany UK/H/1434/001/DC - Germany, France, The Netherlands UK/H/1435/001/DC – Belgium, Germany, France, Italy, The Netherlands UK/H/2331/001/DC – Belgium UK/H/1420/01/DC - Germany UK/H/3086/01/DC - Italy
Procedure Number	UK/H/1416/001/DC (PL 14048/0038) UK/H/1417/001/DC (PL 14048/0041) UK/H/1418/001/DC (PL 14048/0042) UK/H/1434/001/DC (PL 14048/0045) UK/H/1435/001/DC (PL 14048/0040) UK/H/2331/001/DC (PL 14048/0053) UK/H/1420/01/DC (PL 14048/0044) UK/H/3086/01/DC (PL 14048/0065)
End Of Procedure	7th July 2009

Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Levocetirizine dihydrochloride 5 mg film-coated tablets (PL 14048/0040) is as follows. Please note that the SmPCs for PL 14048/0038, PL 14048/0041, PL 14048/0042, PL 14048/0045 and PL 14048/0053 are identical to that below with the exception that they were granted on the 14th October 2009. SmPCs for PL 14048/0044 and PL 14048/0065 are identical to that below with the exception that they were granted on the 30th October 2009.

1 NAME OF THE MEDICINAL PRODUCT

Levocetirizine dihydrochloride 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg levocetirizine dihydrochloride (equivalent to 4.2 mg of levocetirizine).

Excipient: each film-coated tablet contains 64.0 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval, biconvex film-coated tablets, debossed with 'L9CZ' on one side and '5' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levocetirizine is indicated for:

– the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis;
– the relief of symptoms of chronic idiopathic urticaria.

4.2 Posology and method of administration

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food.

Adults and adolescents 12 years and above

The daily recommended dose is 5 mg (one film-coated tablet) once daily.

Children aged 6 to 12 years

The daily recommended dose is 5 mg (one film-coated tablet) daily.
Levocetirizine is not recommended for use in children below age 6 due to insufficient data on safety and efficacy.

Elderly

For the time being, there is no data to suggest that the dose needs to be reduced in elderly patients provided that the renal function is normal.
Patients with moderate to severe renal impairment: there are no data to document the efficacy/safety ratio in patients with renal impairement. Since levocetirizine is mainly excreted via renal route (see section 5.2), in cases no alternative treatment can be used, the dosing intervals must be individualized according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - age(years)]\, x\, weight(kg)}{72\, x\, serum\, creatinine(mg/dl)} (x\, 0.85\ for\ women)$$

Dosing adjustments for adult patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	One tablet daily
Mild	50 – 79	One tablet daily
Moderate	30 - 49	One tablet every two days
Severe	30	One tablet every three days
End-stage renal disease – patients undergoing dialysis	10	Contra-indicated

In pediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance of the patient, his age and his body weight.

Patients with hepatic impairment
No dose adjustment is needed in patients with solely hepatic impairment.

Patients with hepatic impairment and renal impairment
Dose adjustment is recommended (see Patients with moderate to severe renal impairment above).

4.3 Contraindications
Hypersensitivity to levocetirizine, to any of the excipients, to hydroxyzine or to any piperazine derivatives.

Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take levocetirizine film-coated tablets.

4.4 Special warnings and precautions for use
Do not exceed the stated dose.

The use of levocetirizine dihydrochloride is not recommended in children aged less than 6 years since the currently available film-coated tablets do not yet allow dose adaptation.

At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol is taken concomitantly.

Caution in epileptic patients and patients at risk of convulsions is recommended.

4.5 Interaction with other medicinal products and other forms of interaction
Due to the pharmacokinetic, pharmacodynamic and tolerance profile of levocetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.

4.6 Pregnancy and lactation
Very rare clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant or breast feeding women because levocetirizine passes into breast milk.

4.7 Effects on ability to drive and use machines
Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 5 mg.
Patients intending to drive, engaging in potentially hazardous activities or operating machinery should not exceed the recommended dose and should take their response to the medicinal product into account. In these sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

4.8 Undesirable effects

The frequency of undesirable effects has been defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders			Hypersensitivity	Anaphylactic shock
Psychiatric disorders	Somnolence	Agitation	Aggression Confusion Depression Hallucination Insomnia	Tic
Nervous system disorders	Dizziness Headache	Paraesthesia	Convulsions Movement disorders	Dysgeusia Syncope Tremor Dystonia Dyskinesia
Eye disorders				Accomodation disorder Blurred vision Oculogyration
Cardiac disorders			Tachycardia	
Respiratory, thoracic and mediastinal disorders	Pharyngitis Rhinitis*			
Gastrointestinal disorders	Abdominal pain Dry mouth Nausea	Diarrhoea		
Hepatobiliary disorders			Hepatic function abnormal (increased transaminases, alklaline phosphatise, γ-GT and bilirubin)	
Skin and subcutaneous tissue disorders		Pruritus Rash	Urticaria	Angioneurotic oedema Fixed drug eruption
Renal and urinary disorders				Dysuria Enuresis
General disorders and administration site conditions	Fatigue	Asthenia Malaise	Oedema	
Investigations			Weight increased	

* in children

4.9 Overdose

Symptoms

Symptoms observed after an overdose of levocetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect.

Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor and urinary retention.

Management of overdoses
There is no known specific antidote to levocetirizine.
Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence.
Levocetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives, ATC Code: R06A E09

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.
Binding studies revealed that levocetirizine has high affinity for human H1-receptors (Ki = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l). Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

The pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials:

In a study comparing the effects of levocetirizine 5mg, desloratadine 5mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p<0.001$) compared with placebo and desloratadine.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. Levocetirizine inhibits the histamine-mediated early phase of the allergic reaction and also reduces the migration of certain inflammatory cells and the release of certain mediators associated with the late allergic response.

The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis or perennial allergic rhinitis.

The paediatric safety and efficacy of levocetirizine tablets has been studied in two placebo controlled clinical trials including patients aged 6 to 12 years and suffering from seasonal and perennial allergic rhinitis, respectively. In both trials, levocetirizine significantly improved symptoms and increased health-related quality of life.

In a placebo-controlled clinical trial including 166 patients suffering from chronic idiopathic urticaria, 85 patients were treated with placebo and 81 patients with levocetirizine 5mg once daily over six weeks. Treatment with levocetirizine resulted in significant decrease in pruritus severity over the first week and over the total treatment period as compared to placebo. Levocetirizine also resulted in a larger improvement of health-related quality of life as assessed by the Dermatology Life Quality Index as compared to placebo.

Pharmacokinetic / pharmacodynamic relationship
5 mg levocetirizine provides a similar pattern of inhibition of histamine-induced wheal and flare as 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations.

ECGs did not show relevant effects of levocetirizine on QT interval.

5.2 Pharmacokinetic properties

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution:

No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.

Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O- dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.

Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

Elimination

The plasma half-life in adults is 7.9 ± 1.9 hours. The mean apparent total body clearance is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Renal impairment

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Cellulose microcrystalline
Magnesium stearate (E572)

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from moisture

6.5 Nature and contents of container
PVC/PVDC:Al blisters or oPA/Al/PVC:Al blisters

Pack sizes:
Blisters containing 7, 10, 14, 15, 20, 21, 28, 30, 40, 50, 56, 60, 70, 90, 100, 112 or 120 tablets
Unit dose blisters containing: 30x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 14048/0038
PL 14048/0040
PL 14048/0041
PL 14048/0042
PL 14048/0045
PL 14048/0053
PL 14048/0044
PL 14048/0065

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/09/2009
14/10/2009
30/10/2009

10 DATE OF REVISION OF THE TEXT
25/09/2009
14/10/2009
30/10/2009

Module 3
PATIENT INFORMATION LEAFLET

CONSILIENT HEALTH Ltd.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levocetirizine dihydrochloride 5 mg film-coated tablets

levocetirizine

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 LEVOCETIRIZINE DIHYDROCHLORIDE 5 MG IS AND WHAT IT IS USED FOR

Levocetirizine is an anti allergic agent. It is used to treat symptoms associated with allergic conditions, such as:
- hay fever
- year round allergies such as dust or pet allergies
- chronic nettle rash

2. BEFORE YOU TAKE LEVOCETIRIZINE DIHYDROCHLORIDE 5 MG

Do not take Levocetirizine dihydrochloride 5 mg if
- you are **allergic (hypersensitive) to levocetirizine, any other related substance, or any of the other ingredients** of Levocetirizine dihydrochloride 5 mg (see section 6, "What Levocetirizine dihydrochloride 5 mg contains")
- you suffer from **severe kidney failure** (less than 10 ml/min creatinine clearance)
- you have been told by your doctor that you have an **intolerance to some sugars**

Take special care with Levocetirizine dihydrochloride 5 mg
- if you suffer from epilepsy or are in any other way at risk of suffering fits. You should ask your doctor for advice.
- If you suffer from kidney failure. You may require a lower dosage and should discuss your situation with your doctor.

Levocetirizine is not recommended in children less than 6 years of age since the currently available film-coated tablets do not allow for dose adaptation.

Taking other medicines
Other medicines may be affected by levocetirizine. They, in turn, may affect how well levocetirizine works.
Please **tell your doctor or pharmacist** if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Levocetirizine dihydrochloride 5 mg with food and drink
Levocetirizine may be taken with or without food.

You should be cautious if you take levocetirizine at the same time as **alcohol**. In sensitive patients the effect of alcohol may be increased or different than expected.

Pregnancy and breast-feeding
No information is available on the safe use of levocetirizine during pregnancy or breast-feeding. When you are pregnant or breast-feeding you **should only use** levocetirizine if there is a clear benefit outweighing the possible risks. Your doctor will make this decision for you.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
In some patients levocetirizine may cause drowsiness, tiredness and exhaustion. If you experience any of these symptoms, then do not drive or operate any machines.

Important information about some of the ingredients of Levocetirizine dihydrochloride 5 mg
These tablets contain **lactose**; if you have been told by your doctor that you have an **intolerance to some sugars** you must not take Levocetirizine dihydrochloride 5 mg (see Section 2, Do not take).

3. HOW TO TAKE LEVOCETIRIZINE DIHYDROCHLORIDE 5 MG

Always take levocetirizine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You should swallow the tablet **whole** with water or another liquid.

The usual dose for adults and children aged 6 years and over is **one tablet daily**.
Children under 6 years of age should not take levocetirizine.

If you suffer from **mild to moderate kidney failure**, your doctor may prescribe a lower dose according to the severity of your kidney disease.

The duration of treatment depends on the type, duration and course of the complaints. Your doctor or pharmacist will advise you on this.

If you take more Levocetirizine dihydrochloride 5 mg than you should
If you have taken more levocetirizine than you should, you may experience the following symptoms: confusion, diarrhoea, dizziness, fatigue, headache, feeling unwell, dilation of the pupils, itching, restlessness, drowsiness, sleepiness, fast heart beat, shaking and difficulty passing urine. Contact your doctor or pharmacist immediately. They may empty your stomach or can take other measures to alleviate the symptoms.

If you forget to take Levocetirizine dihydrochloride 5 mg
Do not take a double dose to make up for a forgotten dose. Skip the missed dose and take the next tablet at the usual time.

If you stop taking Levocetirizine dihydrochloride 5 mg
If you stop the treatment with levocetirizine earlier than foreseen this should not cause any side effects. The symptoms you took levocetirizine for, may reappear however.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, levocetirizine can cause side effects, although not everybody gets them.

Common side effects (occurring in more than 1 in 100 treated patients):
- Sleepiness
- Dizziness
- Headache
- Inflammation of the throat
- Swelling and irritation inside the nose (in children)
- Abdominal pain
- Dry mouth
- Feeling sick
- Tiredness

Uncommon side effects (occurring in more than 1 in 1000, but in less than 1 in 100 treated patients):
- Sensation of tingling or numbness of the skin
- Diarrhoea
- Rash
- Itching
- Feeling of weakness
- Feeling unwell
- Agitation

Rare side effects (occurring in more than 1 in 10,000 but in less than 1 in 1000 treated patients):
- Faster heart beat
- Fits
- Disorders of movement
- Hives
- Swelling of the skin
- Hypersensitivity (allergic reaction)
- Abnormal liver function
- Weight increase
- Aggression
- Confusion
- Depression
- Hallucinations
- Difficulty in sleeping

Very rare side effects (occurring in less than 1 in 10,000 treated patients):
- Reduction in blood platelets, which increases risk of bleeding or bruising
- Changed or diminished taste sensation
- Fainting
- Blurry vision
- Painful urination
- Bedwetting
- Serious allergic reaction which causes swelling of the face or throat
- Local skin reaction
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Shaking
- Muscle disorders
- Jerky movements
- Circular eye movements
- Tic

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.

5. HOW TO STORE LEVOCETIRIZINE DIHYDROCHLORIDE 5 MG

Keep out of the reach and sight of children.

Do not use levocetirizine after the expiry date which is stated on the packaging after 'EXP'. The first two digits indicate the month and the last four digits indicate the year.
The expiry date refers to the last day of that month.

Store in the original package to protect from moisture.

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 Levocetirizine dihydrochloride 5 mg contains
- The active substance is levocetirizine. Each tablet contains 5 mg of levocetirizine dihydrochloride equivalent to 4.2 mg levocetirizine.
- The other ingredients are microcrystalline cellulose, lactose monohydrate, magnesium stearate (core) and hypromellose (E464), titanium dioxide (E171), and macrogol 400 (coating).

What Levocetirizine dihydrochloride 5 mg looks like and the contents of the pack
The film-coated tablets are white to off-white, oval, biconvex tablets, debossed with 'L9CZ' on one side and '5' on the other side.
They are supplied in blister packs of 7, 10, 14, 15, 20, 21, 28, 30, 40, 50, 56, 60, 70, 90, 100, 112 or 120 tablets per box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder: Synthon BV,
Microweg 22, 6545 CM Nijmegen, The Netherlands.

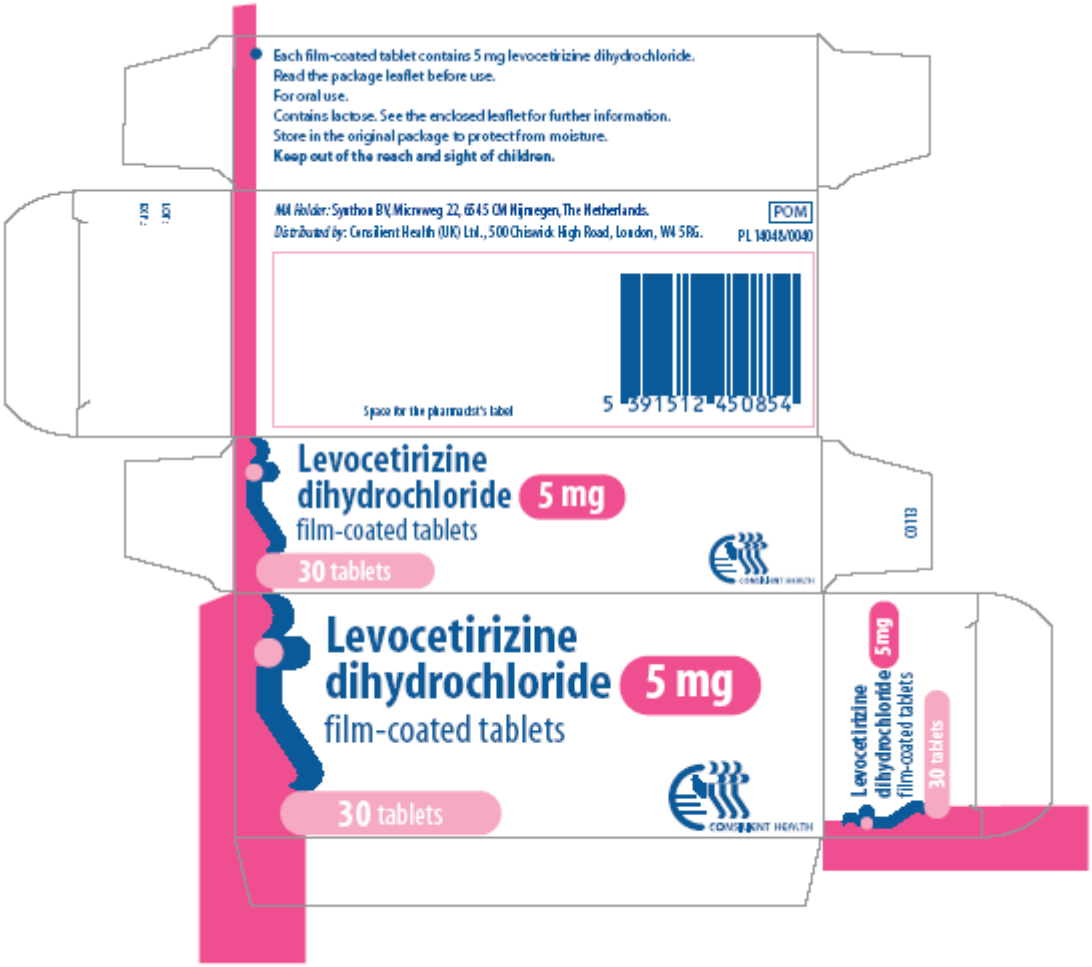
Manufactured by: Synthon Hispania S.L.
Castelló 1, Polígono Las Salinas, 08830 Sant Boi de Llobregat, Spain.

Distributed by: Consilient Health (UK) Ltd,
500 Chiswick High Road, London, W4 5RG.

This leaflet was last revised in September 2009 P0070

Module 4
Labelling

Carton- (PL 14048/0040)



Blister

Carton (PL 14048/0038)

Blister

No mock-ups have been provided for the following licences PL 14048/0041, PL 14048/0042, PL 14048/0045, PL 14048/0053, PL 14048/0044 and PL 14048/0065). The company have committed to providing mock-ups prior to marketing the product.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Levocetirizine dihydrochloride 5 mg film-coated Tablets, for symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria, are approvable.

This application is made under Article 10.3 (hybrid application) of Directive 2001/83 EC, as amended. The application refers to the innovator product, Zyrtec® 10mg (UCB Pharma) that was initially granted a licence in Belgium on 6th November 1986. In CMSs with a 6-year data exclusivity period these applications could have been submitted under Article 10.1 with Xusal/Xyzal as the reference product (in which case the bioequivalence data versus Xusal/Xyzal would have been considered pivotal). However, the Applicant has elected to submit these applications under Article 10.3, with Zyrtek as the reference product - hence the Applicant is relying on the Zyrtec dossier for which data exclusivity has now expired. These applications do not rely on the Xusal/Xyzal dossier which is still subject to data exclusivity in 10-year MSs. This regulatory strategy has been subject to discussions at CMD and is currently considered valid.

Oral anti-histamines, such as cetirizine and levocetirizine, are considered first-line treatment for seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.

Cetirizine is a racemate, comprised of an R- and S-enantiomers. Levocetirizine dihydrochloride is the active (R) enantiomer of the racemate cetirizine dihydrochloride. It is a selective H1 antagonist which inhibits the histamine-mediated early phase of the allergic reaction and also reduces the migration of inflammatory cells and release of mediators associated with the late allergic response.

No new preclinical or clinical efficacy studies were conducted and none are required for an application of this type. The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

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 of 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.

The applications are supported by a bioequivalence study (Study 005) presented by the applicant comparing the pharmacokinetic profile of the test product, levocetirizine dihydrochloride 5 mg film-coated tablets, to that of the reference product, Zyrtek 10mg film-coated tablets (UCB). The RMS has been reassured that the submitted study has been carried out in accordance with GCP, and agreed ethical principles. An additional study (Study 001) was submitted comparing levocetirizine 5 mg film-coated tablets with Xusal® 5mg film-coated tablets. The findings and conclusions of this study could not be considered

in the core assessment for the applications, as the study relates to Xusal, whereas the applications refer to Zyrtec.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Levocetirizine dihydrochloride 5 mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Levocetirizine dihydrochloride
Pharmacotherapeutic classification (ATC code)	Antihistamine for systemic use, piperazine derivative, R06A E09
Pharmaceutical form and strength(s)	Film-coated tablets, 5mg
Reference numbers for the Decentralised Procedure	UK/H/1416/001/DC (PL 14048/0038) UK/H/1417/001/DC (PL 14048/0041) UK/H/1418/001/DC (PL 14048/0042) UK/H/1434/001/DC (PL 14048/0045) UK/H/1435/001/DC (PL 14048/0040) UK/H/2331/001/DC (PL 14048/0053) UK/H/1420/001/DC (PL 14048/0044) UK/H/3086/001/DC (PL 14048/0065)
Reference Member State	United Kingdom
Member States concerned	UK/H/1416/001/DC - Germany, France, Italy, Luxembourg, The Netherlands UK/H/1417/001/DC - Germany UK/H/1418/001/DC - Germany UK/H/1434/001/DC - Germany, France, The Netherlands UK/H/1435/001/DC – Belgium, Germany, France, Italy, The Netherlands UK/H/2331/001/DC – Belgium UK/H/1420/001/DC- Germany UK/H/3086/001/DC - Italy

Marketing Authorisation Number(s)	PL 14048/0038 PL 14048/0041 PL 14048/0042 PL 14048/0045 PL 14048/0040 PL 14048/0053 PL 14048/0044 PL 14048/0065
Name and address of the authorisation holder	Synthon BV Microweg 22 6545 CM Nijmegen The Netherlands

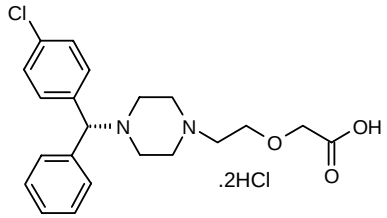
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance

General Information
Nomenclature
(INN): levocetirizine dihydrochloride

Chemical Name:
(R)-(+)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-piperazin-1-yl]ethoxy]aceticacid dihydrochloride

CAS number: 130018-87-0

III.1.2 Structure



Molecular formula: $C_{21}H_{27}Cl_3N_2O_3$
Molecular weight: 461.80 g/mol

III.I.3 General Properties
Levocetirizine dihydrochloride is a white to almost white powder and is freely soluble in water and methanol. Levocetirizine has one chiral centre.

Manufacture
Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Levocetirizine Dihydrochloride is not the subject of a pharmacopoieal monograph but there is a Ph. Eur. monograph for the racemate cetirizine.

An appropriate specification is provided for the active substance levocetirizine dihydrochloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active levocetirizine dihydrochloride is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

P Medicinal Product

Other ingredients consist of pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, magnesium stearate. All ingredients within the core of the tablets comply with their relevant Ph Eur monographs.

The film-coating consists of: hypromellose, titanium dioxide and macrogol 400. All ingredients within the film coating comply with relevant Ph. Eur. monographs.

Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption.

Dissolution and impurity profiles

Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three pilot scales batches of the finished product have been provided and are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch analysis data for three pilot scale batches have been provided and demonstrate compliance with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The product is packaged in blisters composed of either polyvinyl chloride/ polyvinylidene chloride/aluminium (PVC/PVDC:Al) or polyamide/aluminium/polyvinylchloride (oPA/AL/PVC:Al). Specifications and a Certificate of Analysis for the packaging types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 7, 10, 14, 15, 20, 21, 28, 30, 40, 50, 56, 60, 70, 90, 100, 112 or 120 (unit dose blister (30 x 1) tablets. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Stability

Stability testing is performed according to the relevant ICH guidelines. Based on the results of the stability studies, a shelf life of 2 years with the following storage conditions “Store in the original package in order to protect from moisture” has been set; this is acceptable.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
The grant of marketing authorisations is recommended.

III.2 NON CLINICAL ASPECTS

Critical evaluation of the Non-Clinical Overview and Summary

Pharmacodynamic, pharmacokinetic and toxicological properties of cetirizine are well-known. Cetirizine is the racemic mixture of R (levocetirizine) and S cetirizine. Specific pharmacodynamic properties of the pharmacologically active enantiomer, levocetirizine, are described in the literature. As cetirizine / levocetirizine are widely used and well-known substances, no further studies are required and the applicant provides none. An overview based on literature review is thus appropriate.
The non-clinical overview has been written by a suitably qualified person, a registered toxicologist, PhD and dated 7th July 2007. The report refers to 23 publications up to year 2006.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology of levocetirizine and cetirizine is adequate.

Assessor's comment:
The non-clinical overview provides a thorough review of the pharmacology, pharmacokinetics and toxicology of both levocetirizine and cetirizine.

The impurity profile of the proposed product is not discussed in the nonclinical overview. However Module 3 data clarifies that the associated impurities are well controlled and within the limits set out in the ICH guidelines.

The SPC, sections 4.6 and 5.3, are in line with those for the reference product and are therefore acceptable.

Conclusions
There are no objections to approval of Levocetirizine Dihydrochloride 5 mg Tablets from a non-clinical point of view.

III. CLINICAL ASSESSMENT

Introduction
The Clinical Overview has been written by a medically qualified expert and Clinical Research Associate.

The Clinicial Overview contains a succinct summary of the published literature regarding the safety and efficacy of levocetirizine. The Applicant has referred to the Zyrtec dossier for which data exclusivity has expired, but in order to rely upon a bridging bioequivalence study and thence the safety and efficacy data for Zyrtec the Applicant has also demonstrated that there is no clinically relevant difference in safety and efficacy between levocetirizine

and cetirizine and/or that the S-enantiomer (dextrocetirizine) does not contribute to the racemate's therapeutic profile with the following references.

The head-to-head cetirizine versus levocetirizine studies cited by the Applicant were:

1. Baltes et al. Fundam Clin Pharmacol 2001
2. Devalia et al. Allergy 2001
3. Wang et al. Allergy 2001
4. Hindmarch et al. Curr Med Res Opin 2001
5. Garg & Thami. J Derm Treat 2007

With respect to references 1 - 3 the studies upon which these publications are based were conducted as part of the Xusal registration programme. Further to debate between members states during these procedures, references 1-3 were ultimately considered inadmissible being subject to data exclusivity in accordance with discussions at CMDh. The bridging studies initially submitted by the Applicant which were considered during the assessment were therefore references 4 and 5. These are summarised below.

Hindmarch *et al*. Curr Med Res Opin 2001; 17:241-55

Hindmarch and colleagues assessed the CNS and peripheral H1 inhibitory effects of levocetirizine 5mg, cetirizine 10mg, loratadine 10 mg, promethazine 30 mg and placebo in a randomised, double-blind, five-way crossover study. Promethazine was included as a positive internal control given its known effects on psychometric performance. Treatments were administered over a 4-day period with CNS and peripheral treatment-effects assessed on days 1 and 4. CNS effects were assessed via a battery of psychometric tests (critical flicker fusion threshold, choice reaction time, continuous tracking task, line analogue rating scales for sedation) and peripheral effects via the histamine-induced wheal and flare test. Eighteen healthy volunteers provided evaluable data.

No significant effects on any of the CNS measures tested were noted for either levocetirizine or cetirizine in contrast to marked effects with promethazine treatment. With respect to the wheal and flare model, cetirizine and levocetirizine generally had similar effects on wheal and flare, although of note by day 4 attenuation of the initial flare effect (which was noted for all anti-histamines in the study) was much less prominent for cetirizine than levocetirizine - cetirizine was the only anti-histamine in the study to produce notable reduction in flare by day 4.

Table 1: Area under the curve for wheal and flare suppression – change from baseline (mm^2)

	Wheal day 1	Wheal day 4	Flare day 1	Flare day 4
Placebo	-57.09	139.75	1187.38	1909.84
Promethazine	-555.77	-56.38	-203.36	422.71
Loratadine	-264.30	36.13	-203.00	466.62
Cetirizine	-891.08	-908.76	-909.85	-435.06
Levocetirizine	-976.49	-843.66	-908.61	-42.99

A useful diagrammatic presentation in this publication depicts changes in critical flicker fusion threshold (as a measure of CNS activity) compared to wheal suppression (as a measure of intended efficacy) for active treatments versus placebo. The graphics for levocetirizine and cetirizine can be seen to be similar, and in contrast to those associated with either promethazine (not shown) or loratadine.

Figure 1: Change from baseline: wheal suppression and CFF threshold: cetirizine 10 mg, day 1

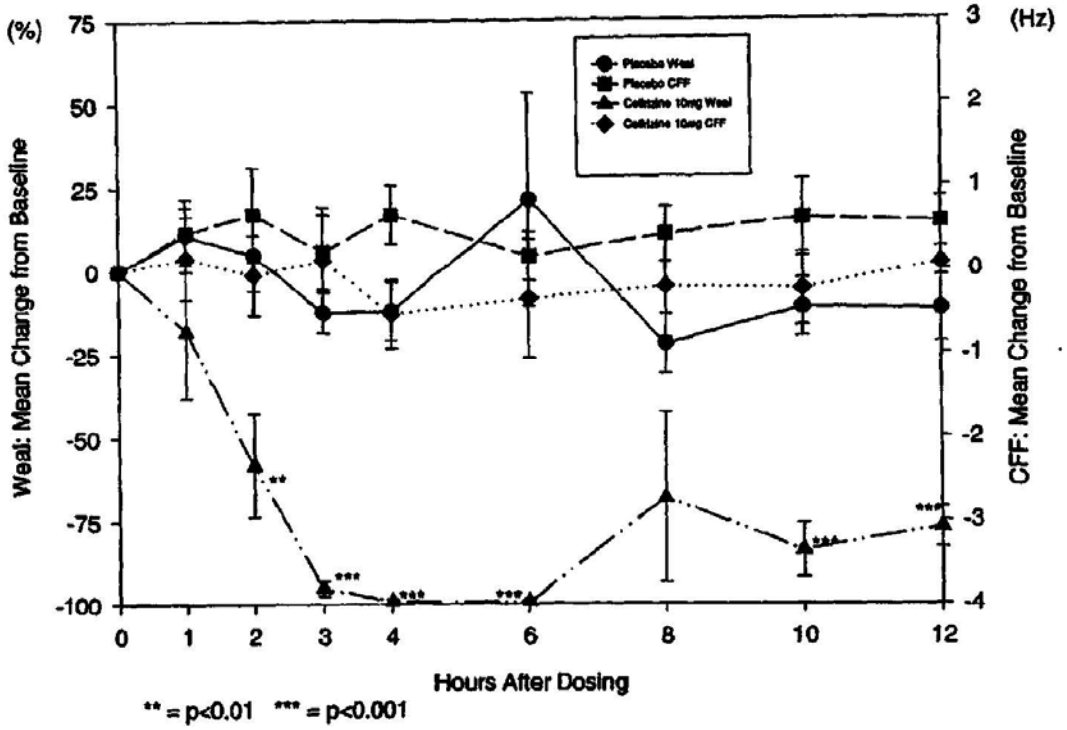


Figure 2: Change from baseline: wheal suppression and CFF threshold: levocetirizine 5 mg, day 1

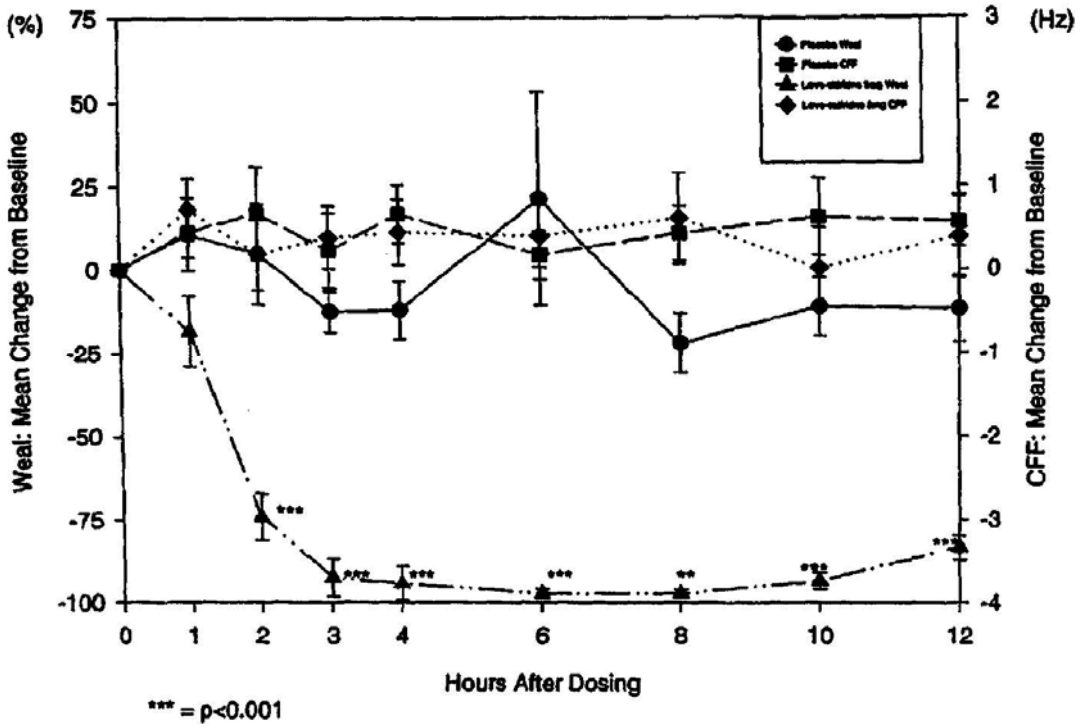
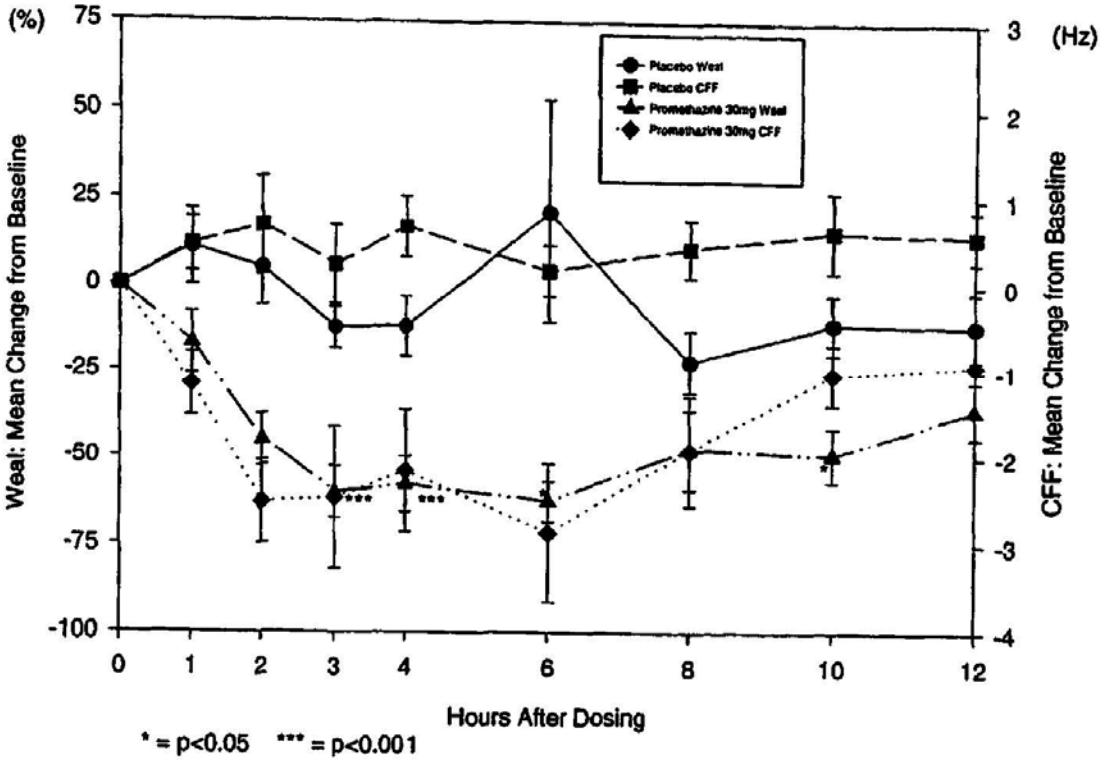


Figure 3: Change from baseline: wheal suppression and CFF threshold: loratadine 10 mg, day 1



Assessor's comment: The key PD study findings are that:

- **Dextrocetirizine makes no clinically relevant contribution to the efficacy of cetirizine (i.e., dextrocetirizine is the distomer) and does not antagonise or modulate the efficacy of levocetirizine (the eutomer), as evidenced by the similarity of levocetirizine and cetirizine effects in a variety PD models.**
- **The PK differences between levocetirizine and cetirizine (e.g., lower volume of distribution of the former, which have been suggested to confer theoretical safety benefits) do not translate to differences in PD.**
- **Levocetirizine was equivalent to cetirizine at a 1:2 dose ratio, there being no consistent evidence across PD trials that either compound was more efficacious**

Garg & Thami. J Derm Treat 2007; 18:23-24
This is the only study in patients which the Applicant has cited.

The study enrolled 45 patients with chronic idiopathic urticaria (CIU) who had showed complete symptomatic control following 6 weeks treatment with cetirizine 10 mg and switched them to 5 mg levocetirizine for 6 weeks. The authors report that wheal and flare responses to both antihistamines were almost equal, but that itch response was 'significantly better with cetirizine'. The authors postulate that this may be related to central effects of cetirizine or effects of the S-enantiomer.

Assessor's comment: This study has major methodological flaws, including selection bias hence major potential for regression to the mean, an open-label design, use of a single sequence only, no accounting for missing data, no detail as to scales used for assessment, no definition of the primary efficacy parameter, etc. As a result these data cannot be interpreted and no conclusions should be drawn from them.

In addition to those references cited by the Applicant, the RMS has identified three other relevant publications which compare the effects of cetirizine and levocetirizine:

1. Prescribe International October 2003
2. Kruszewski et al Pol Merkur Lekarski. 2006 Nov; 21 (125):443-8
3.Kłos et al. Pol Merkur Lekarski. 2006 Nov; 21 (125); 449-53

Assessor's comment: The Applicant should provide a critical assessment of these papers focussing on the key question: Is there any evidence of a difference in effect between cetirizine and levocetirizine.

1. Prescribe International October 2003 Oct; 12 (67): 171-2

This publication describes the only known comparative clinical study of cetirizine and levocetirizine in rhinitis patients. The editorial refers to a double-blind, controlled study comparing a daily dose of cetirizine 10 mg, levocetirizine 5 mg and placebo in 797 patients with seasonal allergic rhinitis aged 12 – 65 years. Patients were treated for one week and assessed on the 4-item TSS scale. The editorial states that *'levocetirizine was equivalent to cetirizine ....and significantly better than placebo'*. Baseline mean T4SS scores were *'just under 8, and treatment reduced scores to a mean level of about 4'*.

Assessor's comment: This editorial though brief provides support for the lack of any clinically relevant difference in the efficacy profiles of levocetirizine and cetirizine, which is in keeping with the PK and PD findings described above.

2. Kruszewski, J., Klos, K., Sulek, K.: Inhibition of histamine-induced wheal, flare and skin blood flow following a single administration of a recommended dose of 10 mg cetirizine, 5 mg desloratadine, 120 and 180 mg fexofenadine, 5 mg levocetirizine and 10 mg loratadine - a randomised, placebo-controlled clinical trial. Pol Merkur Lekarski, 2006

Kruszewski *et al.* compared a number of antihistamine medications in healthy volunteers, who received a histamine-induced skin irritation. The volunteers were randomised into 7 groups of 6 volunteers: 10 mg cetirizine, 5 mg desloratadine, 120 mg fexofenadine, 180 fexofenadine, 5 mg levocetirizine, 10 mg loratadine and placebo. After the skin-provocation with histamine, each volunteer received a single dose of its blinded medication. The influence of the medication was recorded by measuring the size of the wheal and flare, and by measuring the changesin blood-flow in the affected skin area. In all three different

measurements (wheal, flare and blood flow), there is a clear reduction when comparing placebo with the active medications. Levocetirizine and cetirizine showed to be the strongest inhibitors of the histamine-induced irritation. The researchers note that 'levocetirizine inhibited the histamine-induced wheal most strongly and sustainable'. In addition, the authors list the effectiveness of the medications as follows: levocetirizine > cetirizine > fexofenadine 180 = fexofenadine 120 > loratadine = desloratadine. The conclusion of the authors is very clear, and seems to point out that levocetirizine and cetirizine are different in their effectively counteracting a histamine-induced skin provocation. However, the sample sizes used in this study are very small, and it is therefore questionable to what extent this data can be used to distinguish between the efficacy of levocetirzine and cetirizine. This argument gets even stronger when considering the lack of variance-indicators in the figures. All data shown are median data, without variance bars. This raises questions on the validity of making solid conclusions on the efficacy of the separate medications. Lastly, the statistical outcome (p-value) of the comparisions of the separate medications is not noted mentioned anywhere in the article, nor is it mentioned that levocetirizine and cetirizine are significantly different. The only mentioned pvalue refers to the size of the effect needed to become statistically better than placebo. Based on all the above, the Applicant's opinion is that this article lacks the needed information to conclude that there is a difference (or lack thereof) between levocetirizine and cetirizine. Both performed better than the placebo arm, but it is difficult to make further conclusions based on the provided information.

3. Klos, K., Kruszewski, J., Kruszewski, R., Sulek, K.: The effect of 5-days of recommended doses of cetirizine, desloratadine, fexofenadine 120 and 180 mg, levocetirizine and loratadine on histamine-induced skin reaction and skin blood flow - a randomised, double-blind, placebo-controlled clinical trial. Pol Merkur Lekarski, 2006

Klos *et al.* compared a number of antihistamine medications in healthy volunteers, who received a histamine-induced skin irritation. Like in the study by Kruszewski et al., the volunteers were randomised into 7 groups of 6 volunteers: 10 mg/day cetirizine, 5 mg/day desloratadine, 120 mg/day fexofenadine, 180 mg/day fexofenadine, 5 mg/day levocetirizine, 10 mg/day loratadine and placebo. After skin-provocation with histamine, each volunteer received its blinded medication for five consecutive days. The influence of the medication was recorded by measuring the size of the wheal and flare, and by measuring the changes in blood-flow in the affected skin area. In all three different measurements (wheal, flare and blood flow), there is a clear (and significant) reduction when comparing placebo with the active medications. Levocetirizine and cetirizine showed to be the strongest inhibitors of the histamine-induced irritation. The researchers state that 'for the blood flow indicator, the effect of levocetirizine was even stronger ($p>0.04$, the article actually indicates ">") than cetirizine'. In addition, the authors list the effectiveness of the medications as follows: levocetirizine > cetirizine > fexofenadine 180 = fexofenadine 120 > loratadine = desloratadine. Again, the authors draw a clear conclusion by differentiating between levocetirizine and cetirizine. However, the quality of the presented data is questionable. First, the sample sizes are small (only six subjects per treatment arm). In addition, the variation is not mentioned in the article. Lastly, the statement that the effect of levocetirizine is stronger than that of cetirizine has a claimed significance level of $p>0.04$, which suggests lack of significance on this claim. In conclusion, it is difficult to differentiate between cetirizine and levocetirizine based on this article. As a result, it can only be concluded that cetirizine and levocetirizine performed better than placebo. The data that suggest a potential difference between cetirizine and levocetirine seem to lack statistical significance ($p>0.04$).

RMS assessor's conclusion:

Kruszewski *et al:* As the Applicant has noted, in this parallel group study only 6 volunteers were randomised in to each of 7 treatment groups essentially precluding meaningful comparisons between active treatment groups. Moreover, the statistical methods used appear to take no account of baseline reactions which differ between treatment groups. The Applicant's interpretation of the Kruszewski paper is therefore endorsed, i.e., this paper provides no evidence of a difference between cetirizine and levocetirizine and on the contrary appears to suggest they have similar effects. See Figures 4-6:

Figure 4: Median inhibition of histamine induced wheal after a single dose of medication

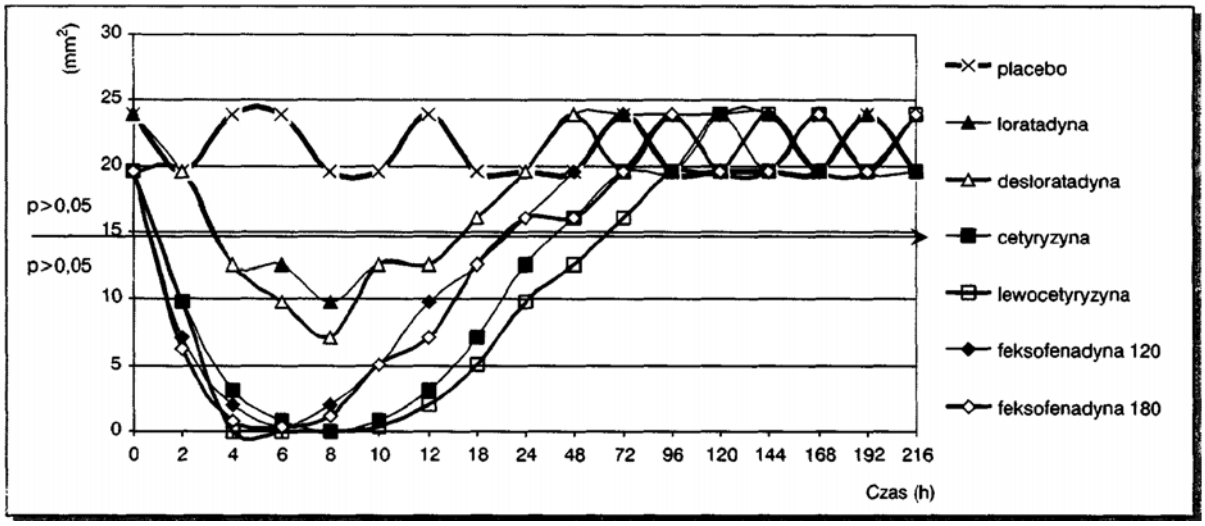


Figure 5: Median inhibition of histamine induced flare after a single dose of medication

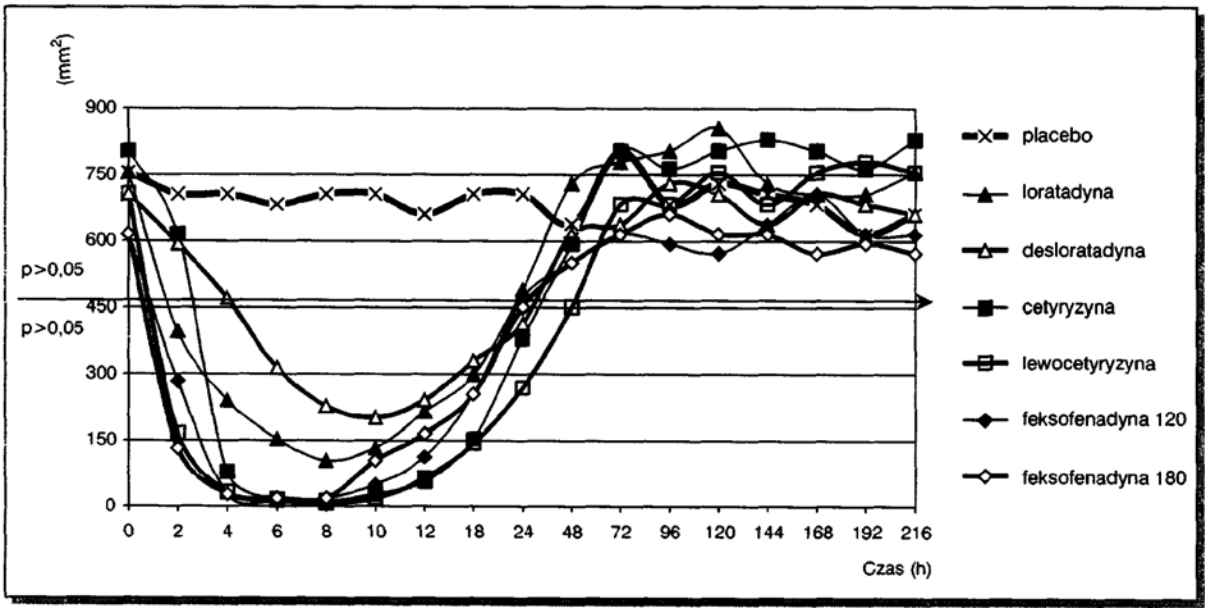
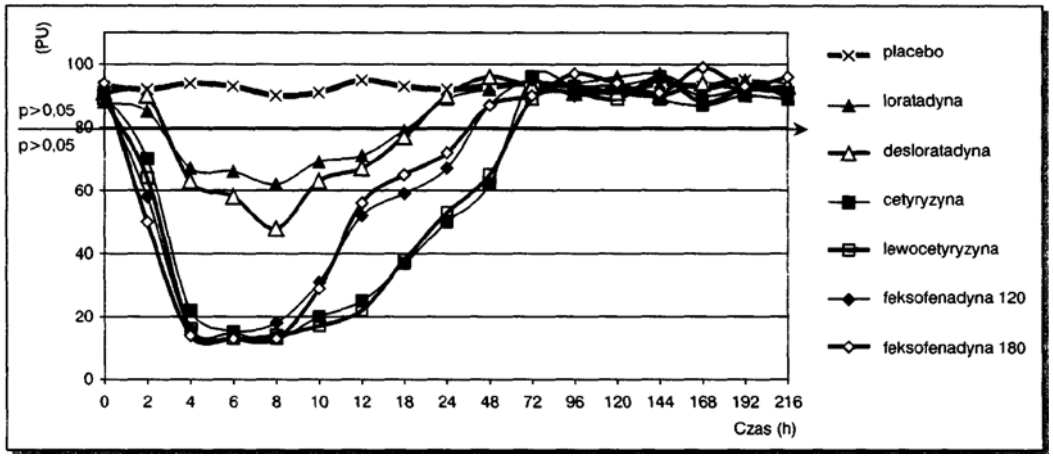


Figure 6: Median inhibition of Laser Doppler flowmetry index after a single dose of medication



Klos *et al:* This study is in essence identical to the Kruszewski study except that study medication was administered for 5 days compared to a single dose. The same flaws in design, statistical methodology and the authors' conclusions are again evident. The data appear to suggest similar effects with levocetirizine and cetirizine – see figures 7-9

Figure 7: Median inhibition of histamine induced wheal after a single dose of medication

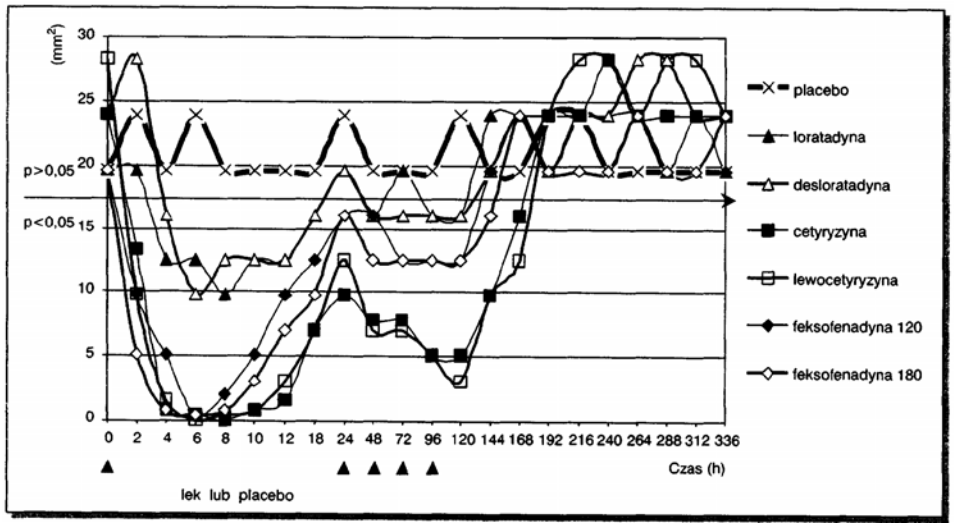


Figure 8: Median inhibition of histamine induced flare after a single dose of medication

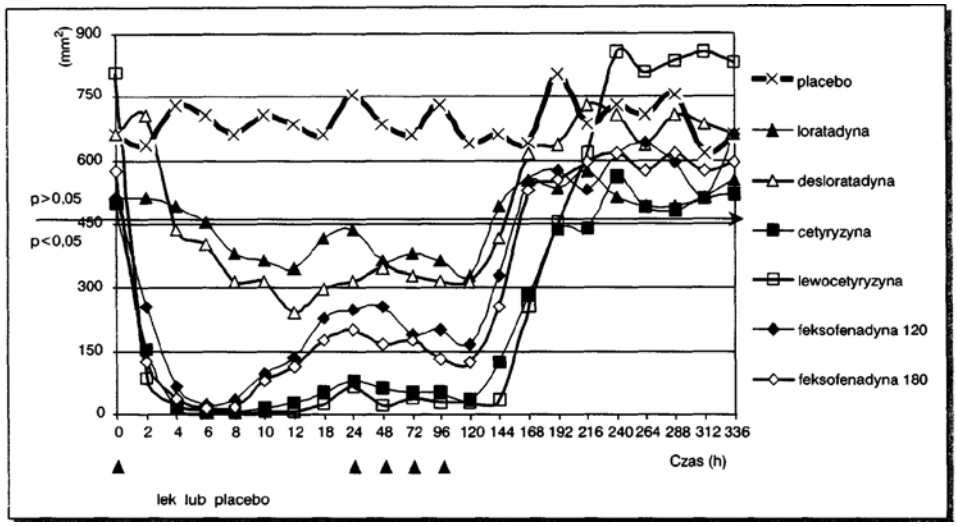
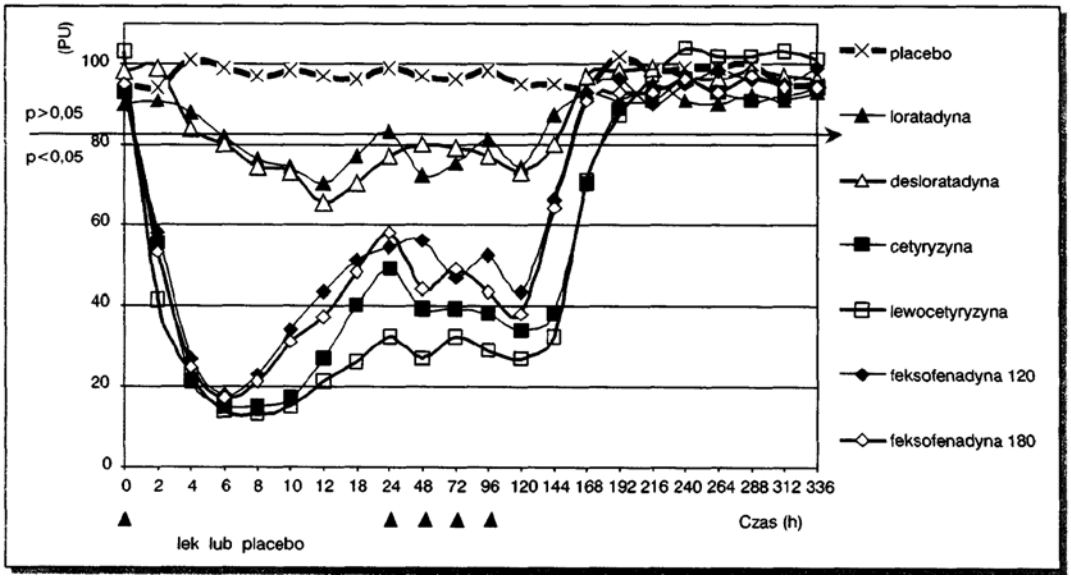


Figure 9: Median inhibition of Laser Doppler flowmetry index after a single dose of medication



In conclusion these two papers generally support the findings of the other pharmacodynamic studies previously discussed.

Assessor overall comment: The Applicant's conclusion that the PK and PD of levocetirizine and cetirizine are similar at a 1:2 dose ratio is endorsed. The Applicant also concludes that the safety and efficacy of levocetirizine and cetirizine are similar. In view of:

- **the Hindmarch publication which supports the lack of any difference with regard to CNS effects between the racemate and R-enantiomer,**
- **the various PD study findings suggesting that differences in clinical efficacy in patients with either rhinitis or urticaria are unlikely,**
- **the Prescrire International editorial summarising the comparative SAR study,**

the Applicant's conclusion is again endorsed. Note that the only clinical study which purports to show an efficacy benefit for cetirizine (Garg, Thami 2007) should be disregarded in view of its major methodolgical flaws.

In conclusion the literature review indicates that there are no clinically relevant differences between levocetirizine and cetirizine.

Clinical study reports

To support the application, the applicant has submitted a bioequivalence study 005.

To support the application, the applicant has submitted two bioequivalence study reports 001 and 005.

Study 001 compared levocetirizine 5 mg film-coated tablets with Xusal® 5mg film-coated tablets. The findings and conclusions of this study could not be considered in the core assessment for the applications, as the study relates to Xusal, whereas the applications refer to Zyrtec.

Study 005 compared levocetirizine 5 mg film-coated tablets with Zyrtec® 10mg film-coated tablets.

Assessor's comment: Study 005 is considered the pivotal study in this application.

Biowaiver
Not applicable

Pharmacokinetic studies

Study 005

Study design
The study was randomized, two-treatment, two-sequence, two-period, cross-over, single-dose and open-label. The analytical sample-processing laboratory was blinded.

Subjects were admitted the day before dose administration and remained at the study centre until the 36 hour blood sample was collected. A washout period of 7 days was observed between the two periods. Subjects fasted overnight for at least 10 hours prior to drug administration. A single dose of the assigned formulation was administered orally.

Single tablet doses of test and reference products were administered to 24 (+ 2 alternate) healthy, adult male and female subjects aged 18 – 55 years under fasting conditions.

Serial blood samples were drawn before dosing and up-to 36 hours after drug administration.

Assessor's comment:
The provision of a fasted study alone is appropriate since the extent of levocetirizine exposure is unaffected by food albeit Tmax is delayed by 1.25 hrs, and Cmax is decreased by about 36% after a high fat meal. These changes in PK do not however have meaningful clinical consequences.

The plasma sampling protocol and washout period are appropriate in view of the known T_{max} (0.9 hours) and elimination half-life (7.9 hours) of the product.

Although at least 13 metabolites of levocetirizine are described, approximately 86% of a dose is excreted unchanged as the parent compound after oral administration. Hence analysis of the parent compound alone is appropriate.

Test and reference products
Test: Levocetirizine dihydrochloride 5 mg tablets; Synthon BV, The Netherlands;

Reference Zyrtec 10mg film-coated; UCB GmbH, Germany;

Population(s) studied
Standard bioequivalence study inclusion and exclusion criteria were employed and were satisfactory.

Analytical methods
The quantitative determination of levocetirizine in human plasma was performed by using both a sensitive and selective chiral HPLC/MS/MS method. Chiral selectivity was established with an internal standard deuterated Cetirizine (racemate), with separation of the two peaks of the internal standard noted on chromatograms which were repeated at the start of each analytical day.

Assessor's comment:

The precision, accuracy, selectivity, recovery, LLOQ, calibration curve range and dilution integrity of the assay are acceptable, as is the stability of the analyte and stock solution under various standard conditions.

Pharmacokinetic Variables

Pharmacokinetic parameters including AUC_{0-t} , $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, $T_{1/2}$, $C_{max}/AUC_{0-\infty}$ were estimated.

Assessor's comment:

PK variables are standard and acceptable

Statistical methods

The drug-concentration-time data were used to calculate the following pharmacokinetic parameters: AUC_{0-t} , $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, $T_{1/2}$, $C_{max}/AUC_{0-\infty}$

The pharmacokinetic parameters were evaluated statistically by an analysis of variance (ANOVA). Statistical model included factors accounting for the following sources of variation: sequence, subjects within sequence, period, and treatment.

Analyses for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were performed both on non-transformed and lntransformed data. In addition, a non-parametric Wilcoxon and median test to Tmax was performed.

For ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} a 90% confidence interval for the ratio of the test to reference means was calculated. The standard bioequivalence acceptance limits of 80% to 125% were used.

Twenty-six (26) subjects were included into the study, twenty-four (24) subjects were planned for analysis and statistical evaluation.

Assessor's comment:

Statistical methods are standard and acceptable

Results - Study 005

A total of 26 subjects were enrolled, all of whom completed the study. Per the protocol data for 24 subjects were analyzed.

All subjects had zero plasma levels of levocetirizine at the start of both periods.

No period or sequence effects were noted

The 95% confidence intervals for $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} test-reference ratios all fulfilled bioequivalence criteria.

Table 2. Geometric LSmeans and 90% CIs for key pharmacokinetic parameters

Treatment	AUC_T ng.hr/ml	AUC_∞ ng.hr/ml	C_{max} ng/ml
Test	1548.4	1609.5	192.2
Reference	1527.7	1587.9	197.5
***T/R Ratio (90% CI)**	101.36 (97.46 - 105.41)	101.36 (97.66 - 105.21)	97.35 (93.35 - 101.52)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

Assessor's comment:
The use of PK data from only 24 subjects was consistent with the protocol.

Zero plasma concentration levels of levocetirizine at the start of period 2 in all cases and a comparison of AUC_{o-t} and $AUC_{0-\infty}$ values, confirm the adequacy of the washout period and sampling duration, respectively.

90% confidence intervals of the test/reference ratios for Ln-transformed C_{max}, AUC_{o-t} and $AUC_{0-\infty}$ fulfilled average bioequivalence criteria.

In conclusion, bioequivalence has been adequately demonstrated.

Pharmacokinetic conclusion – Study 005

The test product levocetirizine dihydrochloride 5 mg film-coated tablets (Synthon BV) and reference Zyrtek 10mg film-coated tablets (UCB) are bioequivalent with respect to the eutomer.

Pharmacodynamic studies
N/A

Additional data
N/A

Post marketing experience
No post-marketing data is available. The medicinal product has not been marketed in any country. However, levocetirizine and cetirizine have a well-recognised safety and efficacy profile.

Benefit-Risk assessment
The application contains an adequate review of published clinical data and bioequivalence has been shown.

The risk:benefit of the product is considered favourable from a clinical and non-clinical perspective.

Grant of a Marketing Authorisation is recommended.

V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Levocetirizine dihydrochloride 5 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence data has been demonstrated between the applicant's Levocetirizine dihydrochloride 5 mg film-coated tablets and Zyrtec® 10mg film-coated tablets (UCB GmbH, Germany).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with levocetirizine dihydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome