RISK MANAGEMENT PLAN (RMP)

Levocetirizine 5 mg, film-coated tablets

Active substance (INN or common name):	Levocetirizine dihydrochloride
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative (R06A E09)
Name of Marketing Authorisation Holder or Applicant:	Glenmark Pharmaceuticals Europe Limited Laxmi House, 2-B Draycott Avenue, Kenton, Harrow, Middlesex, HA3 0BU, United Kingdom
Number of medicinal products to which this RMP refers:	01
Products concerned:	Levocetirizine 5 mg, Film-coated tablets

Data lock point for this RMP	17-Oct-2016	Version number	V1.1
Date of final sign off	19-Apr-2017		

Signatory Page

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Overview of versions:
Version number of last agreed RMP:

Version number	V1.0
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Administrative information on the RMP

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	SVIII Summary of the safety concerns	19-Apr-2017	V1.1
Part III Pharmacovigilance Plan		19-Apr-2017	V1.1
Part IV Plan for post-authorisation efficacy studies		19-Apr-2017	V1.1
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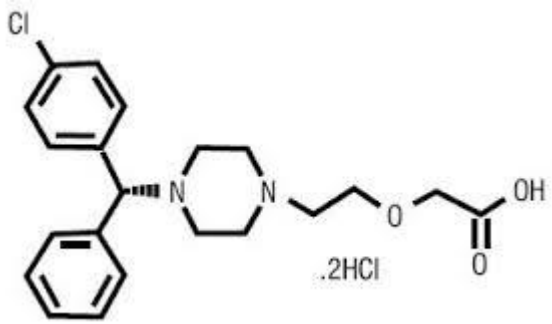
	ANNEX 3 Worldwide marketing status by country	19-Apr-2017	V1.1
	ANNEX 4 Synopsis of on-going and completed clinical trial programme	Not applicable	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not applicable	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	Not applicable
	ANNEX 8 Protocols for studies in Part IV	Not applicable	Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable
	ANNEX 11 Mock up examples	Not applicable	Not applicable
	ANNEX 12 Other supporting data (References)	19-Apr-2017	V1.1

Invented name of medicinal product	Levocetirizine 5 mg, Film-coated tablets
Authorisation procedure	Decentralised
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	The drug substance is a white to off white crystalline powder. *Polymorphism:* levocetirizine Dihydrochloride does not exhibit polymorphism. *Isomerism:* levocetirizine Dihydrochloride has one chiral centre and exhibits Isomerism. *Hygroscopicity:* levocetirizine Dihydrochloride is slightly hygroscopic in nature Molecular formula: $C_{21}H_{27}Cl_3N_2O_3$ Structure:  <u>Mechanism of action</u> 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.
Indications Current	Levocetirizine 5 mg film-coated tablets are indicated in the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 6 years and above.

Posology and route of administration
Current

Posology

Adults and adolescents 12 years and above:

The daily recommended dose is 5 mg (1 film-coated tablet).

Older population aged 65 years and above:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Patients with renal impairment below).

Children aged 6 to 12 years:

The daily recommended dose is 5 mg (1 film-coated tablet).

For children aged 2 to 6 years no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirizine

Adult patients with renal impairment:

The dosing intervals must be individualised 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:

$$\text{CLcr (ml/min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for women})$$

Dosing Adjustments for Patients with Impaired Renal Function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	1 tablet once daily
Mild	50 – 79	1 tablet once daily
Moderate	30 – 49	1 tablet once every 2 days
Severe	< 30	1 tablet once every 3 days
End-stage renal disease - Patients undergoing dialysis	< 10-	Contra-indicated

In paediatric 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 and his body weight. There are no specific data for children with renal impairment. *Patients with hepatic impairment:* No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Patients with renal impairment above). *Duration of use:* Intermittent allergic rhinitis (symptoms experienced for less than four days a week or for less than four weeks a year) has to be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear. In case of persistent allergic rhinitis (symptoms experienced more than four day a week or for more than four weeks a year), continuous therapy can be proposed to the patient throughout the period of exposure to allergens. There is clinical experience with the use of 5 mg levocetirizine as a film-coated tablet formulation currently available for at least 6-month treatment period. In chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate. *Method of administration* The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.
Pharmaceutical form and strengths proposed	Film-Coated Tablet, 5 mg

Country and date of first authorisation worldwide	Germany, 03-Jan-2001

Country and date of first launch worldwide	Unknown

Country and date of first authorisation in the EEA	Germany, 03-Jan-2001

Is the product subject to additional monitoring? ☐ Yes ☒ No

Part II: Module SV - Post-authorisation experience

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

No actions related to safety were taken by regulatory authorities and/or marketing authorisation holder for levocetirizine.

SV.2 Non-study post-authorisation exposure

Cumulatively approximately 1,515,206,360 mg of levocetirizine has been sold worldwide until data lock point 17 October 2016, which equates to an estimated post-marketing exposure of 303,041,272 patient-days or 830,250 patient years. The patient exposure data is calculated using the World Health Organisation (WHO) Defined Daily Dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The WHO DDD for levocetirizine is 5 mg per day.

$$\text{Patient exposure (patient-days)} = \frac{\text{Quantity of levocetirizine sold (mg)}}{\text{Defined Daily Dose (mg/day)}}$$

The estimated exposure is presented region wise in the table below.

Region-wise Estimated Patient Exposure data until data-lock point.

Region	**Total product sold (mg)**	**Estimated Patient exposure in Patient Days (Patient Years)**
Asia	164,673,850	32,934,770 (90232)
Africa	37,019,330	7,403,866 (20285)
European Union	191,743,320	38,348,664 (105065)
Latin America	4,844,600	968,920 (2655)
Commonwealth of Independent States (CIS)	47,121,210	9,424,242 (25820)
Middle East and North Africa (MENA)	51,823,050	10,364,610 (28396)
United States	1,017,981,000	203,596,200 (557798)
Worldwide	**1,515,206,360**	**303,041,272 (830250)**

SV.3 Post-authorisation use in populations not studied in clinical trials

None identified.

SV.4 Post-authorisation off-label use

Two instances of post-authorisation off-label usage were retrieved from MAH database.

Off-label use			
Off label category	**Country**	**Source of Information**	**Comment**
Bronchial asthma	India	Literature	This is a literature case report derived from a scientific study pertaining to a 26-year-old female patient who was treated with levocetirizine (strength and manufacturer unknown) for bronchial asthma.
Mast cell activation syndrome	Germany	Spontaneous (medically unconfirmed)	This is a spontaneous case report, reported by a male patient (age unknown) who was taking levocetirizine 5 mg tablets for mast cell activation syndrome and showed improvement in 70% of the symptoms.

SV.5 Epidemiological study exposure

None

Part II: Module SVIII - Summary of the safety concerns

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions • Sedation (fatigue, somnolence)
Important potential risks	• Psychiatric disorders (paradoxical excitation, depression, suicidal ideation) • Convulsion • Liver injury • Urinary retention
Missing information	• Safety in children below 6 years of age • Safety in breastfed infants exposed to maternal medication • Safety during pregnancy

Part III: Pharmacovigilance Plan

The objective of the MAH's pharmacovigilance strategy is to systematically collect Adverse Drug Reactions (ADRs) from multiple sources and to conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals. Early detection of safety signals enables the MAH to develop and implement appropriate risk management strategy and to detect and evaluate changes in reporting frequency of adverse events (AEs) and changes in overall adverse event pattern suggestive of potential new safety concerns.

Moreover, the pharmacovigilance system put in place ensures that all pharmacovigilance system activities are managed according to the pharmacovigilance legislative requirements. All working procedures within the pharmacovigilance system are controlled as per local applicable guidelines, rules and regulations.

The routine pharmacovigilance practices comply with the pharmacovigilance practices covered in the applicable regulatory guideline. Details of the system and processes in place to achieve the regulations are detailed in the Pharmacovigilance Standard Operating Procedures (SOPs).

III.1 Safety concerns and overview of planned pharmacovigilance (PhV) actions

Table 2: Important identified risks

Hypersensitivity reactions		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Sedation (fatigue, somnolence)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Table 3: Important Potential Risks

Psychiatric disorders (paradoxical excitation, depression, suicidal ideation)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Convulsion		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Liver injury		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Urinary retention		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Table 4: Missing information

Safety in children below 6 years of age		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Safety in breastfed infants exposed to maternal medication		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

Safety during pregnancy		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	To monitor and determine any increase in the incidence and/or nature, severity or changes in outcome in the population at risk.

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Not applicable

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

Not applicable

III.4 Details of outstanding additional pharmacovigilance activities

Not applicable

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable since this is a generic product.

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy study is planned for Levocetirizine 5 mg, film-coated tablets. The available medical literature and the routine pharmacovigilance activities are considered sufficient to evaluate the benefit-risk of the product.

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Table 5: Important Identified Risks

Safety concern	**Hypersensitivity reactions**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and healthcare professionals (HCPs).
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: Hypersensitivity to the active substance, to cetirizine, to hydroxyzine or to any of the excipients listed in **Section 4.3: Contraindications** Information regarding adverse reactions related to hypersensitivity reactions from post-marketing experience is provided in **Section 4.8: Undesirable effects** **PIL:** **Section 2: What you need to know before you take [Name-To be completed nationally]** **Section 4: Possible side effects**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported individual case study reports (ICSR) concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	Frequency of events related to risk remains stable or shows decline relative to exposure.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Sedation (fatigue, somnolence)**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.7: Effects on ability to drive and use machines** **Section 4.8 Undesirable effects:** **PIL:** **Section 4: Possible side effects**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Table 6: Important Potential Risks

Safety concern	**Psychiatric disorders (paradoxical excitation, depression, suicidal ideation)**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.8 Undesirable effects:** **PIL:** **Section 4: Possible side effects**
	Other routine risk minimisation measures:

Safety concern	**Psychiatric disorders (paradoxical excitation, depression, suicidal ideation)**
	Prescription only medicine.
Additional risk minimisation measures	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Convulsion**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.8 Undesirable effects:** **PIL:** **Section 4: Possible side effects**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable

Safety concern	**Convulsion**
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Liver injury**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.8 Undesirable effects:** **PIL:** **Section 4: Possible side effects**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Urinary retention**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.4 Special warnings and precautions for use** **Section 4.8: Undesirable effects**

Safety concern	**Urinary retention**
	PIL: **Section 2: What you need to know before you take [Name-To be completed nationally]** **Warnings and Precautions**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Table 7: Missing Information

Safety concern	**Safety in children below 6 years of age**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.4: Special warnings and precautions for use** **Section 4.8: Undesirable effects** **PIL:** **Section 2: What you need to know before you take [Name-To be completed nationally]** **Children**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None

Safety concern	**Safety in children below 6 years of age**
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Safety in breastfed infants exposed to maternal medication**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.6: Fertility, pregnancy and lactation** **PIL:** **Section 2: What you need to know before you take [Name- To be completed nationally]** **Pregnancy, breast-feeding and fertility**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported ICSRs concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Safety during pregnancy**
Objective(s) of the risk minimisation measures	To minimise risk by communicating the safety concern to patients and HCPs.
Routine risk minimisation measures	Information regarding the risk is provided in: **SmPC**: **Section 4.6: Fertility, pregnancy and lactation** **PIL:** **Section 2: What you need to know before you take [Name- To be completed nationally]** **Pregnancy, breast-feeding and fertility**
	Other routine risk minimisation measures: Prescription only medicine.
Additional risk minimisation measures	None

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Frequency of reported individual case study reports (ICSR) concerning the safety concern will be determined relative to exposure as part of routine signal detection processes.
Criteria for judging the success of the proposed risk minimisation measures	No new signals detected relating to this risk.
Planned dates for assessment	With each RMP update
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

V.2 Risk minimisation measure failure (if applicable)

Not Applicable

V.3 Summary table of risk minimisation measures

Table 8: Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Hypersensitivity reactions	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.3: Contraindications • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Sedation (fatigue, somnolence)	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.7: Effects on ability to drive and use machines • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Important Potential Risks		
Psychiatric disorders (paradoxical excitation, depression, suicidal ideation)	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Convulsion	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Liver injury	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Urinary retention	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Missing Information		
Safety in children below 6 years of age	The information regarding this safety concern is mentioned in the following section(s) of the SmPC:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	
Safety in breastfed infants exposed to maternal medication	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.6: Fertility, pregnancy and lactation Information is provided in PIL for patients. Prescription only medicine.	None
Safety during pregnancy	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.6: Fertility, pregnancy and lactation Information is provided in PIL for patients. Prescription only medicine.	None

Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the Public Assessment Report (PAR)

VI.1.1 Summary table of Safety concerns

Table 9: Summary of safety concerns for PAR

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions • Sedation (fatigue, somnolence)
Important potential risks	• Psychiatric disorders (paradoxical excitation, depression, suicidal ideation) • Convulsion • Liver injury • Urinary retention
Missing information	• Safety in children below 6 years of age • Safety in breastfed infants exposed to maternal medication • Safety during pregnancy

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

No post-authorisation efficacy studies are on-going/planned since the active substance has well established use.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Hypersensitivity reactions	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.3: Contraindications • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Sedation (fatigue, somnolence)	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.7: Effects on ability to drive and use machines • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Potential Risks		
Psychiatric disorders (paradoxical excitation, depression, suicidal ideation)	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Convulsion	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Liver injury	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Urinary retention	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Missing Information		
Safety in children below 6 years of age	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects Information is provided in PIL for patients. Prescription only medicine.	None
Safety in breastfed infants exposed to maternal medication	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.6: Fertility, pregnancy and lactation Information is provided in PIL for patients. Prescription only medicine.	None
Safety during pregnancy	The information regarding this safety concern is mentioned in the following section(s) of the SmPC: • Section 4.6: Fertility, pregnancy and lactation Information is provided in PIL for patients. Prescription only medicine.	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Allergic rhinitis is an allergic inflammation of the nasal airways that occurs when allergens (e.g. pollen, dust) are inhaled by an individual with a sensitized immune system. The allergen triggers the production of the immunoglobulin IgE that finally causes the release of inflammatory mediators such as histamine. This usually causes sneezing, itchy and watery eyes, swelling and inflammation of the nasal passages, and an increase in mucus production. Rhinitis (and sinusitis) are among the most common medical conditions and are frequently associated. In Western societies, an estimated 10% to 25% of the population have allergic rhinitis, with 30 to 60 million persons being affected annually in the United States. Treatment options include avoiding the allergen, other antihistamines, glucocorticoids given as nasal spray or systemically in severe cases.

Nettle rash (urticatia) is a kind of skin rash characterized by pale red, raised, itchy wheals that can appear anywhere on the surface of the skin. It is frequently caused by allergic reactions; however, there are many nonallergic causes. The reaction is caused by a release of inflammatory mediators, including histamine from cutaneous mast cells that leads to fluid leakage from blood vessels. Acute urticaria lasts less than 6 weeks. Urticaria lasting more than 6 weeks is defined as chronic urticaria, and an etiology is seldom identified. Chronic urticaria may have an autoimmune basis. Urticaria may affect up to 20% of the population at some time in their lives. In half of the patients, psychosocial factors are likely to contribute to the development of chronic urticaria. Treatment options include awareness of individual triggers, other antihistamines or systemic corticoids in severe cases.

VI.2.2 Summary of treatment benefits

Levocetirizine 5 mg is an antiallergic medication for the treatment of signs of illness (symptoms) associated with:

- allergic rhinitis (including persistant allergic rhinitis);
- nettle rash (urticaria).

VI.2.3 Unknowns relating to treatment benefits

The safety of Levocetirizine 5 mg has not been established in children under 6 years of age, breastfed infants exposed to maternal medication and during pregnancy.

VI.2.4 Summary of safety concerns

Table 10: Important identified risks

Risk in Lay Language (Clinical Term)	What is known	Preventability
Allergic reactions (Hypersensitivity reactions)	There is a possibility of developing allergic reaction(s) (that might include swelling of the mouth, tongue, face and/or throat, breathing or swallowing difficulties, hives, sudden fall in blood pressure leading to collapse or shock) if a person is hypersensitive to levocetirizine or other ingredients of the formulation.	Levocetirizine 5 mg should be discontinued promptly and appropriate treatment should be initiated in case of an allergic reaction.
Sleepiness, tiredness (Sedation [fatigue, somnolence])	Tests have shown no effects on mental alertness, the ability to react or the ability to drive in healthy people after taking levocetirizine in the	Patients intending to drive, engage in potentially hazardous activities or operate machinery should take their individual response to the

Risk in Lay Language (Clinical Term)	What is known	Preventability
	recommended dosage; however, based on clinical experience, fatigue, somnolence, and sleep disorders occurred commonly (≥1/100 to <1/10). Caution should be exercised when driving or operating machinery.	medicinal product into account and take actions to prevent the side-effects if needed.

Table 11: Important Potential risks

Risk in Lay Language (Clinical Term)	What is known
Mental disorders (opposite excitatory effect, depression, suicidal thought) (Psychiatric disorders [paradoxical excitation, depression, suicidal ideation])	The frequency of incidence of suicidal ideation and depression could not be established from available data. Children may initially show excitation and restlessness after taking Levocetirizine.
Fits (Convulsion)	The frequency of incidence of convulsion could not be established from available data.
Liver damage (Liver injury)	The frequency of incidence of abnormal liver function test could not be established from available data.
Inability to urinate (Urinary retention)	Levocetirizine may increase the risk of urinary retention; however, the frequency of incidence of urinary retention could not be established from available data.

Table 12: Missing information

Risk in Lay Language (Clinical Term)	What is known
Safety in children below 6 years of age	The use of levocetirizine is not recommended in children aged less than 6 years as the clinical safety has not been established.
Safety in breastfed infants exposed to maternal medication	For this medicinal product no clinical data on usage during breast-feeding are available.
Safety during pregnancy	For this medicinal product no clinical data on usage during pregnancy are available.

VI.2.5 Summary of risk minimisation measures by safety concern

The SmPC of Levocetirizine 5 mg, film-coated tablets, provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimising them.

This medicinal product has no additional risk minimisation measures for any of mentioned safety concerns.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

VI.2.7 Summary of changes to the Risk Management Plan over time

Changes to the Risk Management Plan over time is provided in the table below.

Version	Date of sign-off	Safety Concerns	Comments
1.0	15 Jun 2016	**Important identified risks** 1. Hypersensitivity to levocetirizine or to other piperazine derivatives 2. Use in patients with renal impairment 3. Suicidal ideation 4. Urinary retention in patients with predisposing factors e.g. prostatic hyperplasia 5. Lactose intolerance **Important potential risks** 1. CNS depression and sedation with concomitant use of other CNS depressants, including alcohol 2. Overdose **Missing information** 1. Use during pregnancy and lactation 2. Use in children with renal impairment	First version of the RMP.
1.1	dd Apr 2017	**Important identified risks** • Hypersensitivity reactions • Sedation (fatigue, somnolence) **Important potential risks** • Psychiatric disorders (paradoxical excitation, depression, suicidal ideation) • Convulsion • Liver injury • Urinary retention **Missing information** • Safety in children below 6 years of age • Safety in breastfed infants exposed to maternal medication • Safety during pregnancy	List of safety concerns updated based on the comments in Type II variation Preliminary Variation Assessment Report (PT/H/0250/001/II/014) received from the Agency (PT, DE, IE). All relevant sections of the RMP updated. RMP aligned as per generic application and sections updated per latest Glenmark template. Addition of data in Part II: Module SV – Post-authorisation exposure. Minor formatting, style, and grammatical changes done in the RMP.

Part VII: Annexes

Annex 2: SmPC & Package Leaflet

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Name -To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg levocetirizine dihydrochloride.

Excipients: 60.27 mg lactose per tablet.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White oval film coated biconvex tablets, one side embossed with G breakline G and the other side plain. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Name -To be completed nationally] 5 mg film-coated tablets are indicated in the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 6 years and above.

4.2 Posology and method of administration

Posology
Adults and adolescents 12 years and above:
The daily recommended dose is 5 mg (1 film-coated tablet).

Older population aged 65 years and above:
Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Patients with renal impairment below).

Children aged 6 to 12 years:
The daily recommended dose is 5 mg (1 film-coated tablet).

For children aged 2 to 6 years no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirizine

Adult patients with renal impairment:
The dosing intervals must be individualised 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:

$$\text{CLcr (ml/min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} (\times 0.85 \text{ for women})$$

Dosing Adjustments for Patients with Impaired Renal Function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	1 tablet once daily
Mild	50 – 79	1 tablet once daily
Moderate	30 – 49	1 tablet once every 2 days
Severe	< 30	1 tablet once every 3 days
End-stage renal disease - Patients undergoing dialysis	< 10-	Contra-indicated

In paediatric 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 and his body weight. There are no specific data for children with renal impairment.

Patients with hepatic impairment:
No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Patients with renal impairment above).

Duration of use:
Intermittent allergic rhinitis (symptoms experienced for less than four days a week or for less than four weeks a year) has to be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear. In case of persistent allergic rhinitis (symptoms experienced more than four day a week or for more than four weeks a year), continuous therapy can be proposed to the patient throughout the period of exposure to allergens.
There is clinical experience with the use of 5 mg levocetirizine as a film-coated tablet formulation currently available for at least 6-month treatment period. In chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate.

Method of administration
The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

4.3 Contraindications

Hypersensitivity to the active substance, to cetirizine, to hydroxyzine or to any of the excipients listed in section 6.1

.

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

4.4 Special warnings and precautions for use

Paediatric population
The administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended.

The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of levocetirizine

Precaution is recommended with intake of alcohol (see section 4.5. Interactions).

Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with antipyrine, pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam). A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

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

In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, and may cause additional reductions in alertness and impairment of performance.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data (more than 1000 pregnancy outcomes) on pregnant women indicate no malformative or feto/ neonatal toxicity.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

The use of levocetirizine may be considered during pregnancy, if necessary

Breast-feeding
Cetirizine, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

Fertility
For levocetirizine no clinical data are available

4.7 Effects on ability to drive and use machines

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive.

Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with Levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.

4.8 Undesirable effects

Clinical studies
*Adults and adolescents above 12 years of age:*In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6 % of these adverse drug reactions were mild to moderate.
In therapeutic trials, the drop out rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.

Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the drug at the recommended dose of 5 mg daily. From this pooling, following incidence of adverse drug reactions were reported at rates of 1 % or greater (common: ≥1/100, <1/10) under levocetirizine 5 mg or placebo:

Preferred Term	**Placebo (n =771)**	**Levocetirizine 5 mg (n = 935)**
Headache	25 (3.2 %)	24 (2.6 %)
Somnolence	11 (1.4 %)	49 (5.2 %)
Mouth dry	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2 %)	23 (2.5 %)

Further uncommon incidences of adverse reactions (uncommon ≥1/1000, <1/100) like asthenia or abdominal pain were observed.
The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1 %) under levocetirizine 5 mg than under placebo (3.1%).

Paediatric Population
In two placebo-controlled studies in paediatric patients aged 6-11 months and aged 1 year to less than 6 years, 159 subjects were exposed to levocetirizine at the dose of 1.25mg daily for 2 weeks and

1.25mg twice daily respectively. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo.

System Organ Class and Preferred Term	**Placebo (n=83)**	**Levocetirizine (n=159)**
Gastrointestinal Disorders		
Diarrhoea	0	3(1.9%)
Vomiting	1(1.2%)	1(0.6%)
Constipation	0	2(1.3%)
Nervous System Disorders		
Somnolence	2(2.4%)	3(1.9%)
Psychiatric Disorders		
Sleep disorder	0	2(1.3%)

In children aged 6-12 years double blind placebo controlled studies were performed where 243 children were exposed to 5mg levocetirizine daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of adverse drug reactions was reported at rates of 1% or greater under levocetirizine or placebo.

Preferred Term	Placebo (n=240)	Levocetirizine 5mg (n=243)
Headache	5(2.1%)	2(0.8%)
Somnolence	1(0.4%)	7(2.9%)

Post-marketing experience

Adverse reactions from post-marketing and clinical experience are per MedDRA, System Organ Class and per frequency.
The following terminologies have been used in order to classify the occurrence of undesirable effects:

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)

SYSTEM ORGAN CLASS	**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
Immune system disorders					Hypersensitivity including anaphylaxis
Metabolism and nutrition disorders					Increased appetite

SYSTEM ORGAN CLASS	**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
Psychiatric disorders	Headache[1,2], somnolence[1,2] Sleep disorders[1]				Aggression, agitation, insomnia, suicidal ideation hallucination depression
Nervous system disorders					Convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia
Ear and labyrinth disorders					Vertigo
Eye disorders					Visual disturbances, blurred vision
Cardiac disorders					Palpitations Tachycardia
Respiratory, thoracic and mediastinal disorders					Dyspnoea
Gastrointestinal disorders	Dry mouth[1]	Constipation[1] abdominal pain[1],			Nausea vomiting diarrhoea[1]
Hepatobiliary disorders					Hepatitis
Renal and urinary disorders					Dysuria, urinary retention
Skin and subcutaneous tissue disorders					Angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
Musculoskeletal, connective tissues, and bone disorders					Myalgia, Arthalgia
General disorders and administration site conditions	Fatigue[1]				oedema
Investigations					Weight increase, abnormal liver function test

[1] Adverse events from clinical experience.
[2]: incidence from clinical experience in children aged 6-12 years

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

a) Symptoms
Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children.

b) 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 short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative, ATC code: R06A E09.

Mechanism of action
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 effects
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. A pharmacodynamic experimental study *in vivo* (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

Clinical efficiency and safety
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, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies.

A 6-month clinical study in 551 adult patients (including 276 levocetirizine-treated patients) suffering from persistent allergic rhinitis (symptoms present 4 days a week for at least 4 consecutive weeks) and sensitized to house dust mites and grass pollen demonstrated that levocetirizine 5 mg was clinically and statistically significantly more potent than placebo on the relief from the total symptom score of allergic rhinitis throughout the whole duration of the study, without any tachyphylaxis. During the whole duration of the study, levocetirizine significantly improved the quality of life of the patients.

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.

Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, levocetirizine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria.

Pharmacokinetic / pharmacodynamic relationship:
The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

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

Paediatric population
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 children below the age of 6 years, clinical safety has been established from several short- or long -term therapeutic studies:

- one clinical trial in which 29 children 2 to 6 years of age with allergic rhinitis were treated with levocetirizine 1.25 mg twice daily for 4 weeks

- one clinical trial in which 114 children 1 to 5 years of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg twice daily for 2 weeks
- one clinical trial in which 45 children 6 to 11 months of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg once daily for 2weeks

- one long-term (18 months) clinical trial in 255 levocetirizine - treated atopic subjects aged 12 to 24 months at inclusion

The safety profile was similar to that seen in the short-term studies conducted in children 1 to 5 years of age.

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.

In human, 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 half-life is shorter in small children.
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 faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special population

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. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.
Paediatric population

Data from a paediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 6 to 11 years with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean C_{max} was 450 ng/ml, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this paediatric population than in adults. Dedicated pharmacokinetic studies have not been conducted in paediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 324 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Older population (>65 years and above)
Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Gender
Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 ml/min/kg) appears to be comparable to that in men (0.59 ± 0.12 ml/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

Race
The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

Hepatic impairment
The pharmacokinetics of levocetirizine in hepatically impaired subjects have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of the racemic compound cetirizine as a single dose had a 50% increase in half life along with a 40% decrease in clearance compared to healthy 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

Core Tablet
Microcrystalline cellulose
Lactose monohydrate

Silica, colloidal anhydrous
Magnesium stearate
Coating
Opadry Y-1-7000 consisting of:
Hypromellose (E464)
Titanium dioxide (E 171)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blisters and PVC / PVdC – Aluminium blisters

Pack Sizes

10, 20, 21, 28, 30, 50, 90 and 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

Jan 2016

PACKAGE LEAFLET: INFORMATION FOR THE USER

[Name -To be completed nationally]
Levocetirizine dihydrochloride
For adults and children aged 6 years and above

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What [name- to be completed nationally] is and what it is used for

[Name- To be completed nationally] is a type of medicine called a non-sedating antihistamine. It is used to treat signs and symptoms of an allergic reaction such as:
- allergic rhinitis (including persistent allergic rhinitis);
- an itchy rash similar to nettle rash which lasts a long time (urticaria).

2. What you need to know before you take [Name- To be completed nationally]

Do not take [Name- To be completed nationally]
- if you are allergic (hypersensitive) to levocetirizine dihydrochloride, to cetirizine, to hydroxyzine or any of the other ingredients of this medicine (listed in section 6).
-
- If you have **a severe impairment of kidney function** (severe renal failure with creatinine clearance below 10 ml/min)

Warnings and Precautions

Talk to your doctor or pharmacist before taking **[Name- To be completed nationally]**
If you are likely to be unable to empty your bladder (with conditions such as spinal cord injury or enlarged prostate), as levocetirizine may increase the risk of urinary retention, please ask your doctor for advice.

Children

The use of [Name- To be completed nationally] is not recommended in children aged less than 6 years since the currently available film-coated tablets do not allow for appropriate dose adaptation.

Other medicines and [Name- To be completed nationally]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those medicines obtained without a prescription.

[Name- To be completed nationally] with food and drink alcohol
Caution is advised if <Product name> is taken at the same time as alcohol or other agents on the brain.
In sensitive patients, the simultaneous use of cetirizine or levocetirizine and alcohol or other centrally acting agents may have effects on the central nervous system, and may cause additional reductions in alertness and impairment of performance.
Although the racemate cetirizine has been shown not to increase the effect of alcohol

Pregnancy, breast-feeding and fertility
If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, aask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Some patients being treated with [Name- To be completed nationally] may experience drowsiness, tiredness and exhaustion. Use caution when driving or operating machinery until you know how this medicine affects you. However, tests have shown no effects on mental alertness, the ability to react or the ability to drive in healthy people after taking levocetirizine in the recommended dosage.

[Name- To be completed nationally] contains lactose
These tablets contain lactose. If you have been told by your doctor that you have intolerance to some sugars you should contact your doctor before taking them.

3. How to take [name- to be completed nationally]

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for adults and children aged 6 years and over is one tablet daily (5mg).

<Product name> tablets should be swallowed whole with a drink of water. It may be taken with or without food.

Special dosage instructions for specific populations:
Renal and hepatic impairment
Patients whose kidneys do not work very well may be given a lower dose according to the severity of their kidney disease and children the dose will also be chosen on the basis of body weight; the dose will be determined by your doctor.

Patients who have severe impairment of kidney function **must not take** this [name to be completed nationally]

If your liver does not work very well you can still take the recommended prescribed dose.

If both your liver and your kidneys do not work very well, you may be given a lower dose depending on how well your kidneys work and in children the dose will also be chosen on the basis of body weight; the dose will be determined by your doctor

Use in children
In children the dose may be chosen on the basis of body weight; the dose will be determined by your doctor.
. [Name-

To be completed nationally] is not recommended for children under the age of 6 (see Section 2, Warnings and Precautions).
A different formulation is available for children under the age of 6. Please consult your doctor or pharmacist.

For adults and children aged 6 years and over, the tablets should be swallowed whole with water.

Older population aged 65 y and above
No adaptation of the dose is necessary in elderly patients, provided their renal function is normal.

How and when should you take [Name- To be completed nationally]
For oral use only
The tablets should be swallowed whole with a drink of water. It may be taken with or without food.

How long should you take [Name- To be completed nationally]
The duration of use depends on the type, duration and course of your complaints and is determined by your physician

If you take more [Name- To be completed nationally] than you should
A substantial overdose (you take more than you should) may cause somnolence in adults. Children may initially show excitation and restlessness followed by drowsiness.

If you think you have taken an overdose of [Name- To be completed nationally], please tell your doctor immediately who will then decide what action should be taken.

If you forget to take [Name- To be completed nationally]
If you forget to take [Name- To be completed nationally], or if you take a dose lower than that prescribed by your doctor, do not take a double dose to compensate; just wait for the time to take the next dose, and take a normal dose as prescribed by your doctor.

If you stop taking [Name- To be completed nationally]
Stopping treatment should have no negative effects; however, symptoms may return but they should not be any worse than they were prior to treatment with <Product name>.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Hypersensitivity reactions (symptoms may include: swelling of the mouth, tongue, face and/or throat breathing or swallowing difficulties together with hives (angioedema), sudden fall in blood pressure leading to collapse or shock, which may be fatal.) At the first signs of a hypersensitivity reaction, stop taking [Name- To be completed nationally] and see your doctor immediately.

Common side effects (occur in less than 10 users in 100)
- dry mouth
- headache
- tiredness
- somnolence/drowsiness
- sleep disorders

Uncommon side effects (occur in less than 10 users in 1000)
- exhaustion
- abdominal pain
- constipation
-

Not known side effects (cannot be estimated from the available data)

- Increased heart rate
- Palpitations
- convulsions or fits
- pins and needles
- dizziness,
- syncope,
- tremor,
- dysgeusia (distortion of the sense of taste)
- sensation of rotation or movement visual disturbances (such as blurred vision)
- painful or difficult urination,
- inability to completely empty the bladder
- oedema (water retention causing swelling)
- pruritus (itchiness)
- rash
- urticaria(swelling, or outbreak, redness and itchiness of the skin)
- skin eruption
- shortness of breath
- weight increase
- muscular pain
- joint pain
- aggressive or agitated behaviour
- hallucination
- depression
- insomnia,
- recurring thoughts of or preoccupation with suicide, hepatitis (the skin or whites of the eyes may become yellow)
- abnormal liver function test nausea
- vomiting
- increased appetite
- diarrhoea

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [name- to be completed nationally]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after Exp. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Name- To be completed nationally] contains

- The active substance is levocetirizine dihydrochloride
  Each film-coated tablet contains 5 mg levocetirizine dihydrochloride.

- The other ingredients are microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, hypromellose (E464), titanium dioxide (E171), and macrogol 400.

What [Name- To be completed nationally] looks like and contents of the pack
The 5mg film-coated tablets are white, oval, with a G breakline G on one side and the other side is plain. The tablet can be divided into equal doses.
The tablets are packed in either Aluminium/Aluminium blisters or PVC / PVdC – Aluminium blisters

Pack Sizes
10, 20, 21, 28, 30, 50, 90 and 100 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Glenmark Pharmaceuticals Europe Limited,
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex HA3 0BU,
United Kingdom

Manufacturers
Glenmark Pharmaceuticals s.r.o,
Fibíchova 143, 566 17 Vysoké Mýto,
Czech Republic

Tillomed Laboratories Ltd.
3 Howard Road, Eaton Socon, St. Neots,
Cambridgeshire, PE19 8ET
United Kingdom

Glenmark Pharmaceuticals Europe Limited.
Building 2, Croxley Green Business Park,
Croxley Green, Hertfordshire, WD18 8YA,
United Kingdom

<This medicinal product is authorised in the Member States of the EEA under the following names:>

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last approved in {MM/YYYY}.
<[To be completed nationally]>

This leaflet was last revised in Jan 2016

Annex 3 - Worldwide marketing authorisation by country

A3.1 Licensing status in the EEA

Country	Current license status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Austria	Withdrawn	29 Sep 2010	Not available	Levocetirizin Glenmark 5 mg Filmtabletten	Nil
Bulgaria	Valid	13 Apr 2010	Not available	Алерцит 5 mg филмирани таблетки	Nil
Czech Republic	Withdrawn	28 Mar 2012	Not available	Levocetirizin Glenmark 5mg	Nil
	Withdrawn	23 Jun 2010	Not available	Silardex 5 mg potahované tablety	Nil
Denmark	Valid	25 Mar 2010	Not available	Levocetirizin ”Glenmark”	Nil
Estonia	Withdrawn	26 Aug 2011	Not available	Cetizal 5 mg, õhukese polümeerikattega tabletid	Nil
Finland	Valid	24 Aug 2012	Not available	Levocetirizin Glenmark 5 mg tabletti, kalvopäällysteinen	Nil
Germany	Valid	05 Nov 2012	Not available	Levocetirizin Glenmark 5 mg Filmtabletten	Nil
Hungary	Withdrawn	12 Jul 2010	Not available	Cetizal 5 mg filmtabletta	Nil
Ireland	Valid	28 May 2010	Not available	Levocetirizine Glenmark 5mg film-coated tablets	Nil
Latvia	Withdrawn	24 May 2011	Not available	Cetizal 5 mg apvalkotās tabletes	Nil
Lithuania	Withdrawn	08 Jun 2010	Not available	Cetizal 5 mg plévéle dengtos tabletés	Nil
Netherland	Valid	13 Jun 2012	Not available	Levocetirizine dihydrochloride Glenmark 5 mg Filmomhulde Tabletten	Nil
Norway	Withdrawn	02 Dec 2010	Not available	Levocetirizine Glenmark 5 mg Tablett, filmdrasjert	Nil
Poland	Valid	15 Jun 2010	Not available	Lirra, 5 mg, tabletki powlekane	Nil
	Valid	18-Oct-12	Not available	Lirra Gem, 5 mg, tabletki powlekane	Nil

Country	Current license status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Portugal	Withdrawn	8-Apr-14	Not available	Lirragem, 5 mg comprimidos revestidos por película	Nil
	Valid	16-Feb-11	Not available	Levocetirizina Glenmark 5 mg Comprimido revestido por película	Nil
	Valid	16-Feb-11	Not available	Levocetirizina Glenmark 5 mg Comprimido revestido por película	Nil
	Valid	16-Feb-11	Not available	Silardex, 5 mg, Comprimido revestido por pelicula	Nil
	Valid	16-Feb-11	Not available	Levocetirizina Glenmark 5 mg Comprimido revestido por película	Nil
Romania	Valid	4-Oct-10	Not available	Cetizal 5 mg comprimate filmate	Nil
Slovakia	Withdrawn	12-Mar-10	Not available	Cetizal 5 mg	Nil
United Kingdom	Valid	19-Jul-12	Not available	Levocetirizine Glenmark 5 mg film-coated tablets	Nil

A3.2 Licensing status in the rest of the world

Country	Current license status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Dominican Republic	Valid	19 Jan 2015	Not available	Glencet	Nil
Egypt	Valid	6-Feb-11	Not available	Levoctivan Oral Solution	Nil
	Valid	23-Apr-09	Not available	Levoctivan 5 MG Film Coated Tablets	Nil
India	Valid	Not available	Not available	Glenzal Syrup	Nil
	Valid	Not available	Not available	Glencet Tablets	Nil
Jamaica	Valid	26-Nov-14	Not available	Glencet 5mg Film Coated Tablets	Nil

Country	Current license status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Kenya	Valid	Not available	Not available	Glencet Tablets	Nil
Kuwait	Valid	24-Feb-16	Not available	Glencet tablets	Nil
Malaysia	Valid	19-Jan-12	Not available	Glencet Tablets 5mg	Nil
Maldives	Valid	16-Jan-13	Not available	GLENCET TABLET	Nil
Mauritius	Valid	Not available	Not available	Glencet 5MG Tablet	Nil
Myanmar	Valid	30-Sep-13	Not available	Glencet Tablets	Nil
Nepal	Valid	Date is missing.	Not available	Glencet Tablet	Nil
Nigeria	Valid	12-Sep-14	Not available	GLENCET TABLETS	Nil
Philippines	Valid	3-Nov-11	Not available	Glencet Tablets	Nil
Russia	Valid	28-Jul-10	Not available	Glencet	Nil
South Africa	Valid	18-Feb-16	Not available	Glencet 5	Nil
Tanzania	Valid	Not available	Not available	Glencet	Nil
Ukraine	Valid	13-Dec-10	Not available	Glencet	Nil
United Arab Emirates	Valid	6-Oct-13	Not available	Glencet Tablets	Nil
United States	Valid	24-Feb-11	Not available	Levocetirizine Dihyrochloride Tablets	Nil
Venezuela	Valid	24-Nov-11	Not available	Glencet Tablets	Nil

Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part III

Not applicable

Annex 7 - Specific adverse event follow-up forms

Not applicable

Annex 8 - Protocols for proposed and on-going studies in RMP Part IV

Not applicable

Annex 9 - Newly available study reports for RMP Parts III & IV

Not applicable

Annex 10 - Details of proposed additional risk minimisation measures

Not applicable

Annex 11 - Mock-up of proposed additional risk minimisation measures

Not applicable

Annex 12 - Other supporting data

References

1. Addendum to the Clinical Overview dated 09 January 2017.