Summary of Product Characteristics

1. Name of the medicinal product
CETIRIZINE HYDROCHLORIDE TABLETS USP 5 MG

2. Qualitative and quantitative composition
Each film coated tablet contains:
Cetirizine Hydrochloride USP……..5 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form
Tablet

4. Clinical particulars
4.1 Therapeutic indications
Seasonal allergic rhinitis: Cetirizine is indicated for the relief of symptoms associated with seasonal allergic rhinitis (hay fever) in adults and children aged 1-12 years. Symptoms treated effectively include sneezing, rhinorrhoea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing and redness of the eyes.
Perennial allergic rhinitis: Cetirizine is indicated for the relief of symptoms associated with perennial allergic rhinitis in adults and children aged 1-12 years. Symptoms treated effectively include sneezing, rhinorrhoea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.
Chronic idiopathic urticaria: Cetirizine is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children aged 1-12 years. It significantly reduces the occurrence, severity and duration of hives and markedly reduces pruritus. As with other antihistamines, patients should be advised to seek medical advice about the possibility that their urticaria is associated with ingestion of certain foods.

4.2 Posology and method of administration
Cetirizine Tablets
The use of Cetirizine tablets are not recommended in children less than 6 years since this formulation does not allow for appropriate dose adaptation.
Children 6 - 12 years: The recommended dose is 5 mg (half a tablet) twice daily with or without food.
Adults and children over 12 years: The recommended dose is 10 mg (one tablet) once a day, with or without food. The time of administration may be varied to suit individual patient needs.

4.3 Contraindications
- In patients with a known hypersensitivity to any of the ingredients of the Cetirizine formulations.
- In patients with a known hypersensitivity to hydroxyzine (the parent compound of cetirizine) or to any piperazine derivatives
- In patients with severe renal impairment (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 Cetirizine film-coated tablets.

4.4 Special warnings and precautions for use
Concomitant treatment

Although it has been shown that cetirizine at the recommended dose of 10 mg does not potentiate the effect of alcohol, in sensitive patients, the simultaneous administration of cetirizine and alcohol or other CNS depressants may have effects on the CNS. Therefore, precaution is recommended if alcohol is taken concomitantly.

Mental Alertness

Some patients may experience a degree of drowsiness with cetirizine. Studies using objective measurements have shown no effect of cetirizine on cognitive function, motor performance of sleep latency. However, in clinical trials, the occurrence of CNS effects has been observed in some individual patients and due caution should be exercised when driving a car or operating potentially dangerous machinery.

In sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

Epilepsy

CNS stimulation may occur with antihistamines, especially in children. Therefore caution is recommended when treating patients suffering from epilepsy or patients at risk of convulsions.

Renal impairment

Cetirizine clearance is reduced in patients with renal impairment. In patients with renal insufficiency, dosage should be reduced to half the usual recommended dose. Cetirizine is contraindicated in patients with severe renal impairment (less than 10 mL/min creatinine clearance).

Skin and Subcutaneous Tissue

Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) have been reported very rarely with cetirizine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as formation of small pustules occur, with or without pyrexia or erythema, then treatment with cetirizine should be discontinued and a physician should be consulted.

Urinary retention

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

Use in the elderly

There are no data to suggest that elderly who have normal renal function require a lower dose. However, as advancing age may be associated with declining renal function, dosage may need to be reduced in the elderly if creatinine clearance is reduced. Cetirizine is well tolerated by patients 65 years of age and over. Clearance of cetirizine is reduced in proportion to creatinine clearance. In patients whose creatinine clearance is reduced (i.e. those with moderate renal impairment), a dose of 5 mg/day is recommended.

Paediatric use

Cetirizine tablets is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation.

Effects on laboratory tests

No data available

4.5 Interaction with other medicinal products and other forms of interaction

Studies with cetirizine demonstrated that there were no clinically relevant adverse interactions with pseudoephedrine, antipyrine, 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.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Pregnancy Category B2

Reproduction studies in mice, rats and rabbits failed to show evidence of teratogenicity using doses up to 96, 225, and up to 135 mg/kg/day respectively. However, the short half-life of cetirizine in these species suggests that fetal exposure may have been inadequate. In mice, post-natal development was inhibited after 96 mg/kg/day. Clinical data for cetirizine or other compounds of the class are inadequate to establish safety in pregnancy. Until such data are available, cetirizine should be used in pregnancy only if the expected benefits clearly outweigh potential risks to mother and fetus.

Lactation

Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk. Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 those measured in plasma, depending on sampling time after administration. Use of cetirizine in breastfeeding mothers is not recommended.

Effects on fertility

No data available

4.7 Effects on ability to drive and use machines

Although studies using objective measurements have shown no effect of cetirizine on cognitive function, motor performance of sleep latency, due to its potential for sedation, caution should be used when driving a motor vehicle or operating machinery.

In 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 more commonly observed untoward reactions reported during cetirizine administration and not associated with an equivalent incidence among placebo-treated patients are somnolence, dry mouth and fatigue.

The table below shows adverse events occurring with an incidence of greater than 1% after intake of cetirizine 5 to 20 mg cetirizine a day. It pools data obtained from American and European clinical studies (including open studies with access to rescue drug) in urticaria, perennial and seasonal rhinitis. The incidence of somnolence associated with Cetirizine was 14.3% (7.6% under placebo) and was predominantly mild to moderate in severity. After pooling the same studies in the three registered indications, sedation is reported more in the patients suffering from seasonal allergic rhinitis, than in the patients suffering from perennial allergic rhinitis and urticaria.

Adverse experience by WHO grouping	**Number of Patients (%)**	
	Cetirizine (n = 2,487)	**Placebo (n = 1,577)**
Somnolence	356 (14.3%)	120 (7.6%)
Headache	272 (10.2%)	177 (11.2%)
Dry mouth	122 (5.0%)	29 (1.8%)
Fatigue	85 (3.4%)	26 (1.6%)

Nausea	51 (2.1%)	48 (3.0%)
Dizziness	49 (2.0%)	26 (1.6%)
Pharyngitis	34 (1.4%)	15 (1.8%)
Insomnia	29 (1.2%)	17 (1.1%)
Dyspepsia	21 (0.8%)	23 (1.5%)
Pruritus	5 (0.2%)	16 (1.0%)

Assessment of severity of sedation in clinical trials indicates the mild nature of sedation associated with cetirizine.

The following events were observed infrequently (less than 1/100), but more than once, in 2,487 patients who received cetirizine in all US and European trials, a causal relationship with cetirizine administration has not been established. Events are listed in order of decreasing frequency within a given body system.

Autonomic nervous system: Increased appetite, anorexia, flushing, increased sweating.

Cardiovascular: Palpitations/tachycardia.

ENT: Ear ache, epistaxis, altered sense of taste, tinnitus, tongue disorder.

Vision: Eye abnormality, periorbital oedema, abnormal vision, eye pain, conjunctivitis.

Gastrointestinal: Abdominal pain, diarrhoea, vomiting, constipation, flatulence.

Genitourinary: Polyuria, urinary retention, urinary tract infection.

Musculoskeletal: Back pain, myalgia, arthralgia, bone disorder (fracture), leg cramps.

Neurologic: Nervousness, impaired concentration, confusion, paraesthesia, asthenia, hypertonia, tremor.

Respiratory System: Respiratory disorder, coughing, bronchospasm, upper respiratory tract infection, dyspnoea.

Miscellaneous: Weight increase (see comment below), fever, oedema, chest pain, pain, rigors, dysmenorrhoea, thirst, decreased libido.

Weight gain was reported as an adverse effect in 0.4% of cetirizine patients in placebo-controlled trials. In an open study of six months' duration, the mean gain in weight was 2.8% after 20 weeks, with no further increase at 26 weeks. This effect has been reported for other antihistamines.

Occasional instances of reversible liver function test (transaminase) elevations have occurred during cetirizine therapy, without evidence of jaundice, hepatitis or other clinical findings.

Adverse events at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled trials are:

Adverse events (WHO-ART)	Cetirizine (n=1656)	Placebo (n =1294)
Gastro-intestinal system disorders Diarrhoea	1.0 %	0.6 %
Psychiatric disorders Somnolence	1.8 %	1.4 %
Respiratory system disorders Rhinitis	1.4 %	1.1 %
Body as a whole – general disorders Fatigue	1.0 %	0.3 %

Methyl hydroxybenzoate and propyl hydroxybenzoate, included in the oral liquid and oral drops, may cause allergic reactions (possibly delayed).

Post Marketing Data

Adverse drug reactions (ADRs) identified during Post-marketing experience with cetirizine are included in the following table. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10

Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000
Not known	Cannot be estimated from available data

Adverse Drug Reactions Identified During Post-Marketing Experience with Cetirizine by Frequency Category Estimated from Clinical Trials or Epidemiology Studies

SOC Frequency Category	Adverse Event Preferred Term
Immune System Disorders *Not known* *Not known*	 *Anaphylactic shock* *Hypersensitivity*
Psychiatric Disorders *Common* *Not known* *Not known*	 *Insominia* *Agression* *Hallucination*
Nervous System Disorders *Not known*	 *Dysgeusia, dyskinesia, dystonia, memory impariment, syncope, tremor*
Eye Disorders *Not known*	 *Eye pain, eye swelling, vision blurred*
Respiratory, Thoracic and Mediastinal Disorders *Uncommon*	 *Cough*
Gastrointestinal Disorders *Common* *Uncommon*	 *Nausea* *Diarrhoea*
Hepatobiliary Disorders *Not known*	 *Hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)*
Skin and Subcutaneous Tissue Disorders *Uncommon* *Rare* *Not known* *Not known*	 *Pruritus* *Urticaria* *Acute generalised exanthematous pustulosis* *Fixed drug eruption*
Musculoskeletal and Connective Tissue Disorders *Not known*	 *Arthralgia*
Renal and Urinary Disorders *Not known*	 *Enuresis, urinary retention*
Reproductive System and Breast Disorders *Not known*	 *Erectile dysfunction*
General Disorders and Administration Site Conditions *Uncommon* *Not known*	 *Malaise* *Feeling abnormal, pruritus upon withdrawal*

Investigations *Not known*	 *Weight increased*

Adverse Drug Reactions Identified During Post-Marketing Experience with Cetirizine by Frequency Category Estimated from Spontaneous Reporting Rates

SOC Frequency Category	Adverse Event Preferred Term
Immune System Disorders *Very Rare*	 *Hypersensitivity* *Anaphylactic shock*
Nervous system disorders: *Uncommon* *Rare* *Very rare* *Not known*	 *Paraesthesia* *Convulsions* *Dysgeusia, dyskinesia, dystonia, syncope, tremor, memory impairment* *Amnesia*
Musculoskeletal and Connective Tissue Disorders *Very rare*	 *Arthralgia*
Eye disorders *Very Rare*	*Accommodation disorder, blurred vision, oculogyration, eye pain, eye swelling*
Ear and labyrinth disorders *Not known*	 *Vertigo*
Renal and urinary disorders *Very Rare*	 *Dysuria, enuresis, urinary retention*
Skin and subcutaneous tissue disorders *Very rare* *Very rare*	 *Pruritus, rash, urticaria* *Angioneurotic oedema, fixed drug eruption, acute generalised exanthematous pustulosis*
Blood and lymphatic disorders *Very rare*	 *Thrombocytopenia*
Hepatobiliary disorders *Very Rare*	 *Hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)*
Psychiatric disorders *Uncommon* *Rare* *Very rare* *Not known*	 *Agitation* *confusion, depression* *Tic, Aggression, hallucination, insomnia* *Suicidal ideation*
Cardiac disorders *Rare*	 *Tachycardia*
Gastro-intestinal disorders *Very rare*	 *Diarrhoea, nausea*
Respiratory, Thoracic and Mediastinal Disorders *Very rare*	 *Cough*
Reproductive System and Breast Disorders	

Very rare	*Erectile dysfunction*
General Disorders and Administration Site Conditions *Uncommon* *Rare* *Very rare*	 *Asthenia, malaise* *Oedema* *Pruritus upon withdraw, malaise, feeling abnormal*
Investigations *Very Rare*	 *Weight increased*

The following clinically significant adverse events have been reported: cholestasis, glomerulonephritis, haemolytic anaemia, hepatitis, severe hypotension and stillbirth. Data are insufficient to support an estimate of their incidence in the population to be treated.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

Symptoms observed after an overdose of cetirizine are mainly associated with CNS 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.

Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless an agent which is removed by dialysis has been concomitantly ingested.

5. Pharmaceutical properties

5.1 Pharmacodynamic properties

Cetirizine, a human metabolite of hydroxyzine, is an anti-allergic compound; its principal effects are mediated via competitive occupancy of peripheral H_1-receptors.

In vitro receptor binding studies have shown no measurable affinity for receptors other than H_1-receptors.

Clinical trials

Studies in normal volunteers show that cetirizine at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of activity corresponds with the occurrence of maximal plasma levels, and significant blockade persists for at least 24 hours after a single dose. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine, as is cold-induced urticaria. The late phase recruitment of eosinophils, a component of the allergic inflammatory response, is inhibited by cetirizine following cutaneous antigen challenge.

CNS Effects: Autoradiographic studies with radiolabelled cetirizine in the rat have shown very low penetration of the brain. Sedation was observed in animal studies, but only at doses at least 1,000 times greater than those required for antagonism of histamine H_1-receptors. Studies in normal volunteers using objective measurements have, most of the time, shown no effect of cetirizine at the recommended dose of 10 mg on sleep latency time, cognitive function or motor performance. However, the occurrence of CNS effects has been observed in clinical trials in some patients (see Adverse Effects).

Studies using quantitative EEG recordings and various other tests of cognitive function confirmed that cetirizine does not cause CNS depression.

5.2 Pharmacokinetic properties

Absorption

Cetirizine is rapidly absorbed after oral administration. In adults, peak plasma levels after a 10 mg dose are approximately 300 ng/mL and occur at about one hour. Co-administration with food decreases the rate of absorption by 1.7 hour (lower C_{max} and greater T_{max}), but does not affect bioavailability as measured by the AUC. Plasma protein binding is 93%. The bioavailability of cetirizine hydrochloride is similar from the different dosage forms of Cetirizine. The mean time taken to reach the peak serum cetirizine concentration (T_{max}) was 0.67 hour after a single 10 mg dose of the film coated tablets.

Distribution

The apparent volume of distribution is 0.45 L/kg, suggestive of significant extravascular distribution. The plasma elimination half-life in adults is approximately 8 hours and does not change with multiple dosing. Plasma levels are proportional to the dose administered over the range of 5 to 20 mg.

Metabolism

In contrast to other known antihistamines, cetirizine is less extensively metabolised, and approximately 2/3 of an administered dose is excreted unchanged in the urine. This results in high bioavailability with low inter- or intrasubject variation in blood levels. A study using 14-C-labelled cetirizine showed that most of the plasma radioactivity is associated with the parent compound. Only one metabolite has been identified in human plasma, the product of oxidative dealkylation of the terminal carboxymethyl group. The antihistaminic activity of this metabolite is negligible.

Excretion

In children, as with adults, cetirizine is eliminated mostly in the urine. Children over 6 years of age show peak plasma levels and times to peak similar to adults, with slightly more rapid elimination. Children younger than 6 years have more rapid clearance and a shorter half-life relative to adults. The half-life of cetirizine is approximately; 6 hours in children aged 6-12 12 years; 5 hours in children aged 2-6 years, and; 3 hours in infants and toddlers aged 6-24 months.

The total body clearance of cetirizine is reduced in subjects with renal dysfunction but below a creatinine clearance of about 30 to 50 mL/minute, little further change occurs. The pharmacokinetics of the drug was similar in patients with mild impairment (creatinine clearance higher than 40 mL/min) and normal volunteers. Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers. Plasma levels of cetirizine are essentially unaffected by haemodialysis, and the plasma elimination half-life in dialysis patients is approximately 20 hours. The plasma AUC is increased about threefold in these patients. The clearance of cetirizine is reduced in elderly patients, but only in proportion to the decrease in creatinine clearance. Thus, in 16 patients with a mean age of 77 years, half-life increased to 12 hours. Cetirizine blood levels were monitored in a clinical trial of 59 patients, aged 60 to 82, who received 10 mg of cetirizine daily for three weeks, and no undue accumulation of cetirizine was found.

5.3 Preclinical safety data

Genotoxicity

No data available

Carcinogenicity

Carcinogenicity studies over 24 months showed increased incidences of benign liver tumours in male mice (at the maximum dose of 16 mg/kg/day), but not in female mice or in rats.

These benign tumours in mice are commonly found with compounds which cause liver enzyme induction. Since cetirizine does not induce liver enzymes in non-rodents and humans, this may be considered to be a species specific phenomenon. Cetirizine was devoid of mutagenic activity in a series of *in vitro* and *in vivo* assays.
Allergy skin tests are inhibited by antihistamines. Wash-out periods vary in individuals due to different rates of metabolism and different antihistamines. For cetirizine, a wash-out period of at least four days is generally recommended before performing the allergy skin tests.

6. Pharmaceutical particulars

6.1 List of excipients
Maize Starch NF
Povidone USP
Lactose NF
Magnesium Stearate NF
Opadry White (Y-1-7000)
Purified water USP

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30ºC, in a dry place.

6.5 Nature and content of container
Alu-PVC blister of 10's tablets. 10 such blister are packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing authorization holder

UNIQUE PHARMACEUTICAL LABORATORIES
(A Div. of J. B. Chemicals & Pharmaceuticals Ltd.)
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8. Marketing Authorization Number
07892/09500/NMR/2022

9. Date of First Authorization/Renewal of the Authorization
06/10/2022

10. Date of revision of the text
27/07/2023