SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished product:
ARCET SYRUP (Cetirizine Oral Solution BP)

2. Qualitative and Quantitative composition:

COMPOSITION:

Each 5 ml Syrup contains:

Cetirizine Dihydrochloride BP	5 mg
Excipients	q.s.

SR. No	Ingredients
1	Cetirizine Dihydrochloride
2	Sucrose
3	Sorbitol Solution 70%
4	Glycerol
5	Saccharin Sodium
6	Citric Acid Monohydrate
7	Sodium Citrate
8	Methyl Hydroxybenzoate
9	Propyl Hydroxybenzoate
10	Raspberry Red colour
11	Orange Flavour liquid
12	Menthol Crystal
13	Purified Water

3. Pharmaceutical Form: Oral Liquid (Syrup)

4. Clinical Particulars:

4.1 Therapeutic Indications:
Cetirizine is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis. It is also indicated for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria and allergen induced asthma.

4.2 Posology and method of administration:
Adults and Children 6 years and older: 2 teaspoonfuls daily (or 1 teaspoonful twice daily).
Children 2-6 years: 1 teaspoonful once daily or 1/2 teaspoonful twice daily.
Children 6 months - < 2 years: 1/2 teaspoonful once daily. The dose in children 12-23 months of age can be increased to a maximum dose as 1/2 teaspoonful every 12 hours.

4.3 Contraindications:
Hypersensitivity to cetirizine hydrochloride, to any of the excipients used to hydroxyzine or to any piperazine derivatives.
Patients with severe renal impairment at less than 10 ml/min creatinine clearance.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warning and precaution for use:
At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol is taken concomitantly.
Caution should be taken in patients with predisposition factors or urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.
Caution in epileptic patients and patients who are at risk of convulsions is recommended.
Allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

4.5 Interaction with other medicinal products and other forms of interaction:
Due to pharmacokinetic, pharmacodynamic and tolerance profile of cetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).
The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.

4.6 Pregnancy and Lactation:
Pregnancy
For cetirizine very rare clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post natal development. Caution should be exercised when prescribing to pregnant women.

Lactation
Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

4.7. Effects on ability to drive and use machines
Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 10 mg.
Patients intending to drive, engaging in potentially hazardous activities or operating machinery should not exceed the recommended dose and should take their response to the medicinal product into account.
In sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

4.8 Undesirable effects:
Clinical studies have shown that cetirizine at the recommended dosage has minor undesirable effects on the CNS, including somnolence, fatigue, dizziness and headache. In some cases, paradoxical CNS stimulation has been reported.
Although cetirizine is a selective antagonist of peripheral H_1-receptors and is relatively free of anticholinergic activity, isolated cases of micturition difficulty, eye accommodation disorders and dry mouth have been reported.
Instances of abnormal hepatic function with elevated hepatic enzymes accompanied by elevated bilirubin have been reported. Mostly this resolves upon discontinuation of the treatment with cetirizine hydrochloride.
Clinical trials
Double blind controlled clinical trials comparing cetirizine to placebo or other antihistamines at the recommended dosage (10 mg daily for cetirizine), of which quantified safety data are available, included more than 3200 subjects exposed to cetirizine.
From this pooling, the following adverse events were reported for cetirizine 10mg in the placebo-controlled trials at rates of 1.0% or greater.

Adverse event (WHO-ART)	**Cetirizine 10mg (n = 3260)**	**Placebo (n = 3061)**
Body as a whole = general disorders		
Fatigue	1.63%	0.95%
Central and peripheral nervous system disorders		
Dizziness Headache	1.10% 7.42%	0.98% 8.07%
Gastro-intestinal system disorders		
Abdominal pain Dry mouth Nausea	0.98% 2.09% 1.07%	1.08% 0.82% 1.14%
Psychiatric disorders		
Somnolence	9.63%	5.00%

Respiratory system disorders		
Pharyngitis	1.29%	1.34%

Although statistically more common than under placebo, somnolence was mild to moderate in the majority of cases. Objective tests as demonstrated by other studies have demonstrated that usually daily activities are unaffected at the recommended daily dose in healthy young volunteers.

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

Adverse event (WHO-ART)	**Cetirizine 10mg (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%

Post marketing experience

In addition to the adverse effects reported during clinical studies and listed above, the following undesirable effects have been reported in post-marketing experience.

Undesirable effects are described according to MedDRA System Organ Class and by estimated frequency based on post-marketing experience.

Frequencies are defined as follows: 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)

Blood and lymphatic disorders:
Very rare: thrombocytopenia
Immune system disorders:
Rare: hypersensitivity
Very rare: anaphylactic shock
Metabolism and nutrition disorders:
Not known: increased appetite
Psychiatric disorders:
Uncommon: agitation
Rare: aggression, confusion, depression, hallucinations, insomnia
Very rare: tics
Not known: suicidal ideation
Nervous system disorders:
Uncommon: paraesthesia
Rare: convulsions
Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia
Not known: amnesia, memory impairment

Eye disorders:
Very rare: accommodation disorder, blurred vision, oculogyration
Ear and labyrinth disorders:
Not known: vertigo
Cardiac disorders:
Rare: tachycardia
Gastro-intestinal disorders:
Uncommon: diarrhoea
Hepatobiliary disorders:
Rare: hepatic function abnormal (increased transaminases, alkaline phosphatises, γ-GT and bilirubin)
Skin and subcutaneous tissue disorders:
Uncommon: pruritis, rash
Rare: urticaria
Very rare: angioneurotic oedema, fixed drug eruption
Renal and urinary disorders:
Very rare: dysuria, enuresis
Not known: urinary retention
General disorders and administration site conditions:
Uncommon: asthenia, malaise
Rare: oedema
Investigations:
Rare: weight increased

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.

4.9 Overdose

Symptoms

Symptoms observed after an overdose of cetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect. Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

Management

There is no known specific antidote to cetirizine. Should overdose occur symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence. Alternatively consider activated charcoal.
Cetirizine is not effectively removed by dialysis.

5.0 Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives.

ATC Code: R06A E07

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1-receptors.. In vitro receptor binding studies have shown no measurable affinity for other than H_1-receptors.
In addition to its anti-H_1 effect, cetirizine was shown to display anti-allergic activities: at a dose of 10 mg once or twice daily, it inhibits the late phase recruitment of eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.
Studies in healthy volunteers show that cetirizine, at doses of 5 and 10 mg strongly inhibits the wheal and flare reactions induced by very high concentrations of histamine into the skin, but the correlation with efficacy is not established.
In a 35-day study in children aged 5 to 12, no tolerance to the antihistamine effect (suppression of wheal and flare) of cetirizine was found. When a treatment with cetirizine is stopped after repeated administration, the skin recovers its normal reactivity to histamine within 3 days.
In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and concomitant mild to moderate asthma, cetirizine 10mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic patients with mild to moderate asthma.
In a placebo-controlled study, cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of QT interval.
At the recommended dosage, cetirizine has demonstrated that it improves the quality of life of patients with perennial and seasonal allergic rhinitis.

5.2 Pharmacokinetic properties
The steady-state peak plasma concentrations is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h. No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. The distribution of pharmacokinetic parameters such as peak plasma concentration (C_{max}) and area under curve (AUC) is unimodal in human volunteers.
The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased. The extent of bioavailability is similar when cetirizine is given as solutions, capsules or tablets.
The apparent volume of distribution is 0.50 l/kg. Plasma protein binding of cetirizine is 93 ± 0.3%. Cetirizine does not modify the protein binding of warfarin.
Cetirizine does not undergo extensive first pass metabolism. About two thirds of the dose are excreted unchanged in urine. The terminal half-life is approximately 10 hours.
Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.
<u>Special populations</u>
Elderly: Following a single 10 mg oral dose, half life increased by about 50% and clearance decreased by 40% in 16 elderly subjects compared to the normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.
Children, infants and toddlers: The half-life of cetirizine was about 6 hours in children of 6 – 12 years and 5 hours in children 2 – 6 years. In infants and toddlers aged 6 to 24 months, it is reduced to 3.1 hours.
Renally impaired patients: The pharmacokinetics of the drug were similar in patients with mild impairment (creatinine clearance higher than 40 ml/min) and healthy volunteers. Patients with

moderate renal impairment had a 3-fold increase in half-life and 70% decrease in clearance compared to healthy volunteers.
Patients on hemodialysis (creatinine clearance less than 7 ml/min) given a single oral 10 mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normals. Cetirizine was poorly cleared by haemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment.
Hepatically impaired patients: Patients with chronic liver disease (hepatocellular, Cholestatic, and biliary cirrhosis) given 10 or 20 mg of cetirizine as a single dose had a 50 % increase in half life along with a 40 % decrease in clearance compared to healthy subjects.
Dosing adjustment is only necessary in hepatically impaired patients if concomitant renal impairment is present.

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:

Sucrose	BP
Sorbitol Solution 70%	BP
Glycerol	BP
Saccharin Sodium	BP
Citric Acid Monohydrate	BP
Sodium Citrate	BP
Methyl Hydroxybenzoate	BP
Propyl Hydroxybenzoate	BP
Raspberry Red colour	IH
Orange Flavour liquid	IH
Menthol Crystal	BP
Purified Water	BP

6.2 Incompatibilities: Nil

6.3 Shelf Life: 24 months

6.4 Special Precautions for storage:
Do not store above 30°C. Keep out of sight and reach of children.

6.5 Nature and contents of container:
60 ml Amber coloured PET bottle, packed in a printed carton along with pack insert and 5 ml measuring spoon.

6.6 Special precautions for disposal and other handling
None

7. Marketing Authorization Holder:
NIPRO JMI Pharma Ltd.
Unique Heights, Level-6
117, Kazi Nazrul Islam Avenue,
Ramna, Dhaka-1217
Country: Bangladesh

8. Marketing Authorization Number:
06384/07157/NMR/2019

9. Date of first Authorization /renewal of the authorization:
Jul 25, 2021

10. Date of revision of text
May 2018