SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Benadryl Allergy Children's 1mg/ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 1 mg cetirizine dihydrochloride

Excipients:
- one ml of solution contains 580 mg sorbitol (E420)
- one ml of solution contains 51.54 mg propylene glycol (E1520)
- one ml of solution contains 2mg sodium benzoate (E211)
- one ml of solution contains 1.29mg sodium

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution

Clear and colorless liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults and children 2 year and above:

- Cetirizine is indicated for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- Cetirizine is indicated for the relief of symptoms of chronic idiopathic urticaria.

4.2 Posology and method of administration

Children aged from 2 to 6 years: 2.5 mg twice daily (2.5 ml oral solution twice daily (a half spoon twice daily)).

Children aged from 6 to 12 years: 5 mg twice daily (5 ml oral solution bid (a full spoon twice daily)).

Adults and adolescents over 12 years of age: 10 mg once daily (10 ml oral solution (2 full spoons)).

The solution can be swallowed as such.

Elderly subjects: data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

Patients with moderate to severe renal impairment: there are no data to document the efficacy/safety ratio in patients with renal impairment. Since cetirizine is mainly eliminated via renal route (see section 5.2), in cases no alternative treatment can be used, the dosing intervals must be individualized according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in ml/min is needed. The CL_{cr} (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Dosing adjustments for adult patients with impaired renal function

Group	Creatinine clearance (ml/min)	Dosage and frequency

Normal	≥ 80	10 mg once daily
Mild	50 – 79	10 mg once daily
Moderate	30 – 49	5 mg once daily
Severe	< 30	5 mg once every 2 days
End-stage renal disease - Patients undergoing dialysis	< 10	Contra-indicated

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

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

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

4.3. Contraindications

Hypersensitivity to cetirizine dihydrochloride, to hydroxyzine, to any piperazine derivatives, or to any of the excipients listed in section 6.1.

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

4.4. Special warnings and precautions 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.

Patients with liver or kidney disease should consult with a physician before use. The physician should determine if a different dose is needed.

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.

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

The use of the product is not recommended in children aged less than 2 years.

This medicine contains 2.9g sorbitol in each 5ml which is equivalent to 580mg/ml. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and a mild laxative effect. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol

(or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicine contains less than 1mmol sodium (23mg) per 5ml, that is to say essentially 'sodium-free'.

This medicine contains 257.7mg propylene glycol (E1520) in each 5ml dose, which is equivalent to 51.54mg/ml.

This medicine contains benzoic acid 1.6955 mg/ml (1.526-1.865 mg/ml).

Allergy skin tests are inhibited by antihistamines and a wash-out period of 3 days is recommended before performing them.

If symptoms persist or worsen, stop use and consult a physician.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the 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 Fertility, pregnancy and lactation

This product should not be used during pregnancy or breastfeeding unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus or breastfeeding infant.

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/fetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

Lactation
Cetirizine is excreted in human milk at concentrations representing 25% to 90% those measured in plasma, depending on sampling time after administration.

Caution should be exercised when prescribing to breast feeding women because cetirizine passes into breast milk.

4.7. Effects on ability to drive and use machines

Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 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.

Caution should be used when driving a motor vehicle or operating machinery.

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 dihydrochloride.

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 10 mg in the placebo-controlled trials at rates of 1.0 % or greater:

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

Post-marketing experience

In addition to the adverse effects reported during clinical studies and listed above, isolated cases of the following adverse drug reactions 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, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000, <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, hallucination, insomnia
Very rare: tic
Not known: suicidal ideation, nightmares

Nervous system disorders:

Uncommon: paraesthesia
Rare: convulsions, movements disorders
Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia
Not known: amnesia, memory impairment

Eye disorders:
Very rare: accommodation disorder, blurred vision, eye swelling, oculogyration
Not known: eye pain

Ear and labyrinth disorders:
Not known: vertigo

Cardiac disorders:
Rare: tachycardia

Respiratory, thoracic and mediastinal disorders:
Very rare: cough

Gastro-intestinal disorders:
Uncommon: diarrhoea
Very rare: nausea

Hepatobiliary disorders:
Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)
Not known: Hepatitis[a]
a: Including Drug-induced liver injury (DILI) and other types of non-infectious hepatitis.

Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash
Rare: urticaria
Very rare: angioneurotic oedema, fixed drug eruption
Not known: acute generalised exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders:
Not known: arthralgia

Renal and urinary disorders:
Very rare: dysuria, enuresis
Not known: urinary retention

Reproductive system and breast disorders:
Not known: erectile dysfunction

General disorders and administration site conditions:
Uncommon: asthenia, malaise
Rare: oedema
Very rare: feeling abnormal
Not known: pruritus upon withdrawal

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.
Cetirizine is not effectively removed by dialysis.

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07

Mechanism of action

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. *Ex vivo* experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral H_1-receptors.

Pharmacodynamics

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, and the dose of 30mg/day inhibits the influx of eosinophils in the broncho alveolar lavage fluid during a late-phase bronchial constriction induced by allergen inhalation in asthmatic subjects. Moreover, cetirizine inhibits the late–phase inflammatory reaction induced in chronic urticaria patients by intradermal administration of Kallikrein. It also downregulates the expression of adhesion molecules, such as ICAM-1 and VCAM-1, which are markers of allergic inflammation.

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. The onset of activity after a single 10mg dose occurs within 20 minutes in 50% of the subjects and within one hour in 95%. This activity persists for at least 24 hours after a single administration.

In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic 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 10 mg 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

Absorption
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.

Distribution
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.

Biotransformation
Cetirizine does not undergo extensive first pass metabolism.

Elimination
About two third of the dose are excreted unchanged in urine. The terminal half-life is approximately 10 hours.

Linearity
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 (see section 4.2).

Hepatically impaired patients: Patients with chronic liver diseases (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

Sorbitol solution (E420)
Propylene glycol (E1520)
Sucralose liquid concentrate (containing sodium benzoate and potassium sorbate)
Sodium Benzoate (E211)
Citric acid
Tutti-Frutti flavour (containing propylene glycol and flavouring ingredients)
Natural Masking Flavour Type 27872 (containing propylene glycol)
Purified water.

6.2 Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

The container closure system is a 120 ml polypropylene bottle closed with a white polypropylene child resistant cap.

A 20ml dosing cup with lines at 2.5 ml, 5 ml and 10 ml is provided with the bottle.

6.6. Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
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High Wycombe
Buckinghamshire
HP12 4EG
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8 MARKETING AUTHORISATION NUMBER(S)

PL 15513/0138

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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