Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Histek 10 mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cetirizine dihydrochloride 10 mg

Excipients include: lactose monohydrate: 117mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

Film-coated, white or almost white convex, oral shaped, tablets.
Scored on one side. The tablets are marked “C” on one side, “J” and “E” on either side of a central division line on the reverse.

The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of perennial rhinitis, seasonal allergic rhinitis (hay fever) and chronic idiopathic urticaria in adults and children aged 6 years and over.

4.2 Posology and method of administration

For oral use only.

Children aged from 6-12 years: 5mg twice daily (a half tablet twice daily).

Adults and children aged 12 years and over: One 10mg tablet daily.

Elderly patients: 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 ration in patients with renal impairment. Since cetirizine is mainly excreted via renal route (see section 5.2), in case no alternative treatment can be used, 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:

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

Dosing adjustments for adults patients with impaired renal function

Group	Creatinine Clearance (ml/min)	Posology and frequency
Normal	≥ 80	10mg once daily
Mild	50-79	10mg once daily
Moderate	30-49	5mg once daily
Severe	<30	5mg once every two days
End-stage Renal Disease Patients undergoing dialysis	<10	Contraindicated

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.

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).

Method of administration
The tablets need to be swallowed with a glass of liquid.

4.3 Contraindications

Cetirizine is contraindicated in patients who are hypersensitive to cetirizine, hydroxyzine or to any piperazine derivatives, or to any of the excipients of the tablets (listed in section 6.1).

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

4.4 Special warnings and precautions for use

Dosage adjustments are necessary in patients with moderate or severe renal impairment, and in liver impairment (see section 4.2 Posology and method of administration).

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 of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.

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

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

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

Paediatric population
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.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other antihistamines it is recommended that excessive alcohol consumption be avoided.

Concurrent use of cetirizine with other CNS depressants should also be avoided as reduction in alertness and impairment of performance may occur.

No evidence of interactions with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, ketoconazole and pseudoephedrine has been reported. 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

Pregnancy
Very rare clinical data on exposed pregnancies are available for cetirizine. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3 Preclinical Safety Data). Caution should be exercised when prescribing to pregnant women.

Lactation
Cetirizine is excreted in breast milk at concentrations representing 25 – 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

At the recommended dose of 10mg, driving ability, sleep latency, alertness and reaction time have not demonstrated any clinically relevant effects.

Patients intending to perform skilled tasks such as driving, 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.

Concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance (See section 4.8 Undesirable effects).

4.8 Undesirable effects

Clinical studies have shown that cetirizine at the recommended dosage has minor adverse 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.
For those patients who are affected the dosage should be halved and taken twice daily (i.e. take 5mg in the morning and 5mg in the evening).

Instances of abnormal hepatic function with elevated hepatic enzymes accompanied by elevated bilirubin have been reported. Mostly this resolves upon discontinuation of the drug.

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 reactions were reported for cetirizine 10 mg in the placebo-controlled trials at rates of 1.0 % or greater:

Adverse reactions (WHO-ART)	Cetirizine (n=3260)	Placebo (n=3061)
General disorders		
Fatigue	1.63 %	0.95 %
Nervous system disorders		
Dizziness	1.10 %	0.98 %
Headache	7.42 %	8.07 %
Gastrointestinal 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 reactions at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled clinical trials are:

Adverse reactions (WHO-ART)	Cetirizine (n=3260)	Placebo (n=3061)
Gastrointestinal disorders		
Diarrhoea	1.0 %	0.6 %
Psychiatric disorders		
Somnolence	1.8 %	1.4 %
Respiratory system disorders		
Rhinitis	1.4 %	1.1 %
General disorders		
Fatigue	1.0 %	0.3 %

Post-marketing experience

In addition to the adverse reactions 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

Gastro-intestinal disorders:
Uncommon: diarrhoea

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: 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

Hepatobiliary disorders:
Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γGT and bilirubin)

Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash
Rare: urticarial
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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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. Symptoms of overdosage in adults may include drowsiness; in children agitation or restlessness can occur followed by drowsiness. Adverse events reported after 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. Treatment of overdose should be symptomatic and supportive. Gastric lavage should be performed in the case of massive overdosage and should be considered following ingestion of a short occurrence. Cetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07

Cetirizine is a potent antihistamine, with selective H1 receptor antagonist activity. The histamine-mediated ‘early’ phase of the allergic reaction is inhibited by cetirizine, which also reduces the migration of inflammatory cells and the release of mediators associated with the ‘late’ allergic responses. Effects on other receptors are negligible and consequently cetirizine is unlikely to cause undesirable anti-cholinergic and anti-serotonin effects.

Studies in healthy volunteers show that cetirizine, at dose of 5 and 10 mg strongly inhibits the wheal and flare reactions induced by very high concentrations of histamine into the skin, but the correlatoin with efficacy is not established. In a 35-day study in children aged 5 to 12, no tolerance to the anthistaminic effect (supression 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 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.

At the recommended therapeutic dose of 10mg daily, impairment of CNS function has not been found to be greater than with placebo.

5.2 Pharmacokinetic properties

The steady-state peak plasma concentration 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 (Cmax) and area under curve (AUC) is unimodal in human volunteers. Cetirizine is rapidly absorbed from the gastrointestinal tract; absorption is not reduced by food, although the rate may be decreased slightly. The extent of bioavailability is similar when cetirizine is given as solutions, capsules or tablets. Apparent plasma clearance is greater in children than in adults: the terminal elimination half-life in healthy adult volunteers ranges between 6.7-10.7 hours.

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 is mainly excreted unchanged in the urine (approximately 70% over 5 days compared with 10% in the faeces). The terminal half-life is approximately 10 hours.

Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.

Special populations

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 drugs was 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 normal. 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 in conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In studies using rats and rabbits, no evidence of reproductive toxicity was shown at doses at least 20 times the human daily dose.

Long-term studies of 6 months to 1 year have been performed using rats, beagle dogs and monkeys. No-effect levels ranged from 75 to 125 times the recommended clinical dose, depending on species and duration of treatment.

Cetirizine is not carcinogenic *in vitro*, but some mutagenic potential has been observed in *in vitro* studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose monohydrate
Crospovidone
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Macrogol stearate
Cellulose, microcrystalline

Propylene glycol
Titanium dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special requirements.

6.5 Nature and contents of container

Blister packs make from 20µm aluminium and 45µm aluminum packed into a cardboard outer container. HDPE tablet containers.
Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Fannin Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA1457/012/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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