1. NAME OF THE MEDICINAL PRODUCT

Zirtek Plus Decongestant 5 mg/120 mg Prolonged Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet provides 5 mg cetirizine dihydrochloride for immediate release, and 120 mg pseudoephedrine hydrochloride for prolonged release.

Excipients with known effect: one tablet contains 43.23 mg lactose monohydrate

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged release tablet.
White to off-white, round, biconvex circle-embossed, film-coated tablet, having a circular logo on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine-pseudoephedrine is indicated for the treatment of symptoms such as nasal congestion, sneezing, rhinorrhoea, and nasal and ocular pruritus associated with seasonal or perennial allergic rhinitis. Cetirizine-pseudoephedrine should be administered when the anti-allergic properties of cetirizine dihydrochloride and the nasal decongestant activity of pseudoephedrine hydrochloride are desired.

4.2 Posology and method of administration

Posology
Adults
One tablet two times a day (morning and evening), corresponding to the maximum recommended dose of 10 mg of cetirizine dihydrochloride and 240 mg of pseudoephedrine hydrochloride daily.

Special populations

Paediatric population
Adolescents from 12 years of age and above: 1 tablet two times a day (morning and evening), with or without food.

Children under 12 years of age: the use of the product is contraindicated (see sections 4.3 and 4.4).

Renal impairment
The dose should be reduced to 1 tablet daily in patients with moderate renal insufficiency.

Hepatic impairment
The dose should be reduced to 1 tablet daily in patients with moderate hepatic insufficiency.

Duration of treatment
The duration of treatment should not exceed the period of symptoms and should not exceed 2 to 3 weeks at the recommended dose (1 tablet, twice daily).
After disappearance of nasal symptoms, treatment should be continued with an antihistamine alone.

Method of administration
Tablets should be swallowed whole with some liquid, and must not be broken, chewed or crushed. They may be taken with or without food.

4.3 Contraindications

Cetirizine-pseudoephedrine is contra-indicated in patients with:
- known hypersensitivity to the active substances or to any of the excipients listed in section 6.1, to ephedrine or piperazine
- hypertension or ischaemic heart disease
- severe renal insufficiency
- uncontrolled hyperthyroidism
- severe arrhythmias
- pheochromocytoma
- elevated intraocular pressure
- urinary retention
- during administration of antihypertensives such as ß-blockers, sympathomimetics, dihydroergotamine or amphetamines
- during treatment with monoamine oxidase inhibitors (MAOI), up to 2 weeks after their discontinuation
- a history of stroke or increased risk of haemorrhagic stroke. This includes concomitant treatment with vasoconstrictors (e.g. bromocriptine, pergolide, lisuride, cabergoline, ergotamine, dihydroergotamine) or any other decongestant drug (e.g. phenylpropanolamine, phenylephrine, ephedrine) used either by oral route or by nasal route, as vasoconstriction and elevated blood pressure increase the risk of haemorrhagic stroke.

Cetirizine-pseudoephedrine is contraindicated in children under 12 years of age (see section 4.2 and 4.4).

4.4 Special warnings and precautions for use

The physician or pharmacist should reassure himself that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations).

Cetirizine-pseudoephedrine should be used with caution in patients over 50 years of age, patients with diabetes mellitus, hyperthyroidism, tachycardia, cardiac arrhythmia, angina, moderate hepatic or renal insufficiency, prostatic hypertrophy (patient may have increased difficulty with micturition) or urethral dysfunction, in cases of ingestion of alcohol or other central nervous system (CNS) depressants and also in the elderly.

Cetirizine-pseudoephedrine is contraindicated in children under 12 years of age (see section 4.2 and 4.3) because the combination has not been studied in this age group and due to the presence of pseudoephedrine.

Caution should also be exercised in patients with a history of stroke or at high risk of such.

Due to the vasoconstrictor effect of pseudoephedrine, caution is recommended in patients who are at risk for hypercoagulability, as in inflammatory bowel disease.

Caution is also essential in patients taking sympathomimetics (decongestants, anorexigenic substances or psychostimulants such as amphetamines), tricyclic antidepressants, linezolid, guanethidine, reserpine, phenothiazines, antihypertensives (see section 4.5), cardiac glycosides such as digoxin or digitoxin (risk of cardiac arrhythmia).

Caution is required in hypertensive patients who are treated concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), because both pseudoephedrine and NSAIDs can increase blood pressure.

This product may act as a cerebral stimulant giving rise to insomnia, nervousness, hyperpyrexia, tremor and epileptiform convulsions.

As with centrally acting stimulants, cases of abuse have been observed with pseudoephedrine.

At therapeutic doses, no clinically significant interactions of cetirizine have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol or other substances with CNS depressant activity is taken concomitantly with cetirizine-pseudoephedrine

Patients with rare hereditary problems of galactose intolerance, total 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 the combination medicinal product cetirizine-pseudoephedrine.

No clinically significant interaction has been described with cetirizine, but caution is recommended on concomitant use of sedatives.

In a multiple dose study of theophylline (400 mg once a day) and cetirizine, there was a small (16%) decrease in clearance of cetirizine, while exposure to 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 exposure to ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

Concomitant use of cetirizine-pseudoephedrine and MAOI or ß-blockers can cause blood pressure to increase. Given the long duration of action of MAOI, this interaction is still possible 2 weeks after discontinuation of such treatment.

An increase in blood pressure can also occur on concomitant administration of dihydroergotamine or linezolid.

The following combinations are not recommended as there is a risk of vasoconstriction and increased blood pressure: bromocriptine, cabergoline, lisuride, pergolide, as well as dihydroergotamine, ergotamine, methylergometrine, and other vasoconstrictors used as oral or nasal decongestants (phenylpropanolamine, phenylephrine, ephedrine, …).

Sympathomimetic amines can reduce the antihypertensive effect of drugs which interfere with sympathetic activity including methyldopa, α- and β-adrenergic blocking agents.

Tricyclic antidepressants can potentiate the hypertensive effect of pseudoephedrine.

The ectopic activity of a pacemaker can be increased when pseudoephedrine is used with cardiac glycosides, such as digoxin or digitoxin; use of cetirizine-pseudoephedrine is therefore not advised in patients treated with cardiac glycosides.

Antacids and proton pump inhibitors increase the absorption of pseudoephedrine, kaolin reduces absorption.

Concurrent use with halogenated anaesthetic agents such as chloroform, enflurane, isoflurane, cyclopropane, halothane may provoke or worsen ventricular arrhythmia.

The concurrent use of alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance, although cetirizine does not potentiate the effect of alcohol (0.5 g/L blood levels). No negative effects of pseudoephedrine have been reported nor are they expected.

Antihistamines can interfere with cutaneous tests for allergies and an appropriate wash-out period of 3 days is required before conducting such tests.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data on the use of cetirizine-pseudoephedrine in pregnant women. Cetirizine-pseudoephedrine is not recommended during pregnancy.

The use of pseudoephedrine during the first trimester of pregnancy has been associated with an increased frequency of gastroschisis (a developmental defect in the abdominal wall with intestinal herniation) and of small intestinal atresia (congenital obstruction of small intestine). Due to the vasoconstrictive properties of pseudoephedrine, cetirizine-pseudoephedrine should not be used during the third trimester as it can induce a reduction in uteroplacental circulation. Data on a limited number of exposed pregnancies indicate no adverse effects of cetirizine on pregnancy or on the health of the fetus/ newborn child.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Breast-feeding
Cetirizine and pseudoephedrine are excreted into human milk. Therefore, cetirizine-pseudoephedrine is not recommended during breast-feeding.

Fertility
A study in rats did not reveal any impact on fertility at an oral dose of 160 mg/kg (containing 6.4 mg/kg cetirizine and 153.6 mg/kg pseudoephedrine), producing systemic exposure to cetirizine 2 fold higher than the therapeutic exposure in humans (section 5.3). There are no available data on fertility in humans.

Pseudoephedrine affected spermatogenesis in the rat following i.p. administration but the relevance to humans following oral administation is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients intending to drive vehicles, to perform potentially hazardous activities or operating machinery should not exceed the recommended dose and take into account the individual's response to the medicinal product. Patients who experience somnolence should refrain from driving, engaging in potentially hazardous activities or operating machinery.

In patients administered with cetirizine at the approved dose of 10 mg/day, objective measurements of driving ability, sleep latency and assembly line performance, have not demonstrated any clinically relevant effects. Nonetheless, concurrent use of cetirizine with alcohol or other substances with CNS depressant activity may cause additional reductions in alertness and impairment of performance.

No negative effects of pseudoephedrine on the ability to drive and use machines have been reported nor are they expected.

It should nevertheless be noted that variations in these effects exist with different drugs in different individuals: in clinical trials, subjective feelings of somnolence have been reported. At doses higher than normally recommended, central nervous system effects may occur.

4.8 Undesirable effects

Post-marketing experience

The following table lists the undesirable effects by body system and by frequency. The frequencies are defined as follows:

very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

Immune system disorders:
Rare: hypersensitivity reactions (including anaphylactic shock)

Psychiatric disorders:
Common: nervousness, insomnia
Uncommon: agitation, anxiety
Rare: hallucinations
Very rare, including isolated cases: psychotic disorder

Nervous system disorders:
Common: vertigo, dizziness, headache, drowsiness
Rare: convulsions, tremor
Very rare: dysgeusia, cerebrovascular accident (stroke)

Eye disorders:
Not known: accommodation disorder, blurred vision, mydriasis, eye pain, visual impairment, photophobia

Cardiac disorders:
Common: tachycardia
Rare: arrhythmia
Not Known: palpitations

Vascular disorders:
Rare: pallor, arterial hypertension
Very rare: circulatory collapse

Respiratory, thoracic and mediastinal disorders:
Not known: dyspnoea

Gastrointestinal disorders:
Common: dry mouth, nausea
Rare: vomiting
Very rare: colitis ischaemic

Hepatobiliary disorders:
Rare: abnormal hepatic function (elevation in transaminases, alkaline phosphatases, gamma-GT and bilirubin)

Skin and subcutaneous tissue disorders:
Rare: dry skin, rash, sweating increased, urticaria
Very rare: angioneurotic oedema, fixed drug eruption
Not known: acute generalized exanthematous pustulosis

Renal and urinary disorders:

Rare: dysuria

Reproductive system and breast disorders
Not known: erectile dysfunction

General disorders and administration site conditions:
Common: asthenia

Isolated cases of hepatitis have been reported when cetirizine alone is administered.

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

1. Pseudoephedrine

Symptoms:
A severe overdose of pseudoephedrine can cause vomiting, mydriasis, tachycardia, arrhythmia, hypertension, signs of CNS depression (sedation, apnoea, loss of consciousness, cyanosis and cardiovascular collapse) or CNS stimulation (insomnia, hallucinations, tremors, convulsions) that can be fatal.

Treatment:
Treatment for overdose, preferably given in hospital, should be symptomatic and supportive. Consideration should be given to the possible concomitant ingestion of other drugs. If spontaneous vomiting does not occur, it should be induced; gastric lavage is recommended. After vomiting, the drug remaining in the stomach can be absorbed by administration of an aqueous suspension of charcoal. The usual supportive measures should be undertaken, including frequent monitoring of vital signs.

No antidote is known. Sympathomimetic amines should not be used. Hypertension should be controlled with an alpha-adrenergic blocking agent and tachycardia by a beta-adrenergic blocker. Epileptic seizures can be treated with 10 mg of diazepam intravenously (or by 0.5 mg/kg by the rectal route in children).
Cetirizine and pseudoephedrine are poorly eliminated by haemodialysis.

2. Cetirizine

Symptoms:
Sedation can be a symptom of overdose; it appears with a single dose of 50 mg upwards.

Treatment:
At the present time there is no specific antidote.
In the case of massive overdose, gastric lavage should be performed as soon as possible. The usual supportive measures should be undertaken, with frequent monitoring of vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nasal decongestants for systemic use, ATC code: R01B A52

The pharmacodynamic activity of cetirizine-pseudoephedrine is directly related to the effects of its active constituents.

1. Cetirizine:

In animal studies, cetirizine acts as a H1-antagonist devoid of significant anticholinergic and antiserotoninergic effects. In pharmacologically active doses, it induces neither sedation nor behavioural changes, which may be due to the absence of passage through the blood-brain barrier.

In human pharmacological studies, cetirizine has been shown capable of inhibiting some of the effects of exogenous histamine. The onset of this action is rapid. Cetirizine also inhibits the effects of endogenous histamine liberated in vivo by a histamine-releasing agent such as compound 48/80 (synthetic polyamine, condensation product of *N*-methyl-*p*-methoxyphenylethylamine with formaldehyde). In addition, it inhibits the skin reaction induced by VIP (Vasoactive Intestinal Polypeptide) and substance P, both of which are neuropeptides considered to be involved in the allergic reaction. Cetirizine inhibits the histamine-mediated early phase of the allergic reaction. It also significantly inhibits the migration of inflammatory cells (including eosinophils) and the release of mediators associated with the late allergic response.

Moreover, it reduces the allergic reaction caused by specific antigens. These effects are achieved without any objective effect on the central nervous system, either in psychometric tests or in the quantitative EEG.

2. Pseudoephedrine:

Pseudoephedrine, a stereoisomer of ephedrine, is an orally active sympathomimetic, whose alpha-mimetic effects are greater than its beta-mimetic activity; due to its vasoconstrictor action, it has a decongestant effect on the nasal mucosa.
In recommended doses, it can induce other sympathomimetic effects such as a rise in blood pressure, tachycardia or symptoms of central excitation such as insomnia.

5.2 Pharmacokinetic properties

1. Cetirizine:

Cetirizine is rapidly and almost completely absorbed after oral administration. Under fasting conditions, peak plasma concentrations are generally obtained after 1 hour. The degree of absorption is not reduced by the presence of food, but the rate of absorption is slowed and peak concentrations do not appear until 3 hours after administration. Cetirizine is not subject to appreciable metabolism during the first hepatic passage. After repeated oral administration, the daily urinary excretion of unchanged cetirizine is approximately 65% of the administered dose. Absorption and elimination of cetirizine are independent of the dose. The degree of inter- and intra-individual variation is low. The plasma half-life of cetirizine is 9 hours and this value increases in patients with renal insufficiency. Cetirizine is highly bound to plasma proteins (93%).

2. Pseudoephedrine:

Pseudoephedrine is rapidly and completely absorbed after oral administration. Pseudoephedrine in a sustained release form allows maximum plasma concentrations to be reached after 8 hours.

Between a quarter and half of the administered dose of pseudoephedrine is transformed in the liver by N-demethylation into an active metabolite, nor-pseudoephedrine. This metabolite, together with the remaining non-metabolised pseudoephedrine, is excreted in the urine. The rate of urinary excretion is increased if the pH of the urine is decreased and decreased in the case of urinary alkalinisation.
A meal rich in fat does not affect the absorption of pseudoephedrine.

On repeated oral administration (every 12 hours), the steady state is reached after 6 days of treatment and the half-life has been estimated as 15 hours.

3. Combination:

There is no evidence of a significant pharmacokinetic interaction between cetirizine and pseudoephedrine.

5.3 Preclinical safety data

Animal studies have demonstrated no-toxic effect levels at 40 mg/kg/day in the Cynomolgus monkey (3.7- and 1.8-fold human exposure for pseudoephedrine and cetirizine respectively) and at 30 mg/kg/day in the rat (0.6-fold human exposure for pseudoephedrine; ratio for cetirizine unknown).

A no-effect level of 40 mg/kg/day was established in reproduction toxicity studies in the rat. Due to the low level of systemic exposure obtained in this species, these results cannot be considered as demonstrating the safety of use in pregnant and breast-feeding women.

Fertility in male and female rats was unimpaired at oral doses up to 160 mg/kg/day (1:24) in reproduction toxicology studies, which represents a systemic exposure 2- fold the therapeutic exposure in humans to cetirizine. Overall, the cetirizine/pseudoephedrine combination did not

produce any adverse effects on embryo-foetal viability and development of the offspring, at clinically relevant doses. At doses of 160 mg/kg/day in pregnant rats (~7.5- x therapeutic exposure in humans for pseudoephedrine, and around therapeutic exposure for cetirizine) observations included decreased pup survival, a small increase in bone deformations, and delay of some development parameters.

Pseudoephedrine affected spermatogenesis in the rat after i.p. administration at doses 5-fold the maximum human recommended dose based on allometric scaling. Based on oral bioavailability, higher safety margins can be expected following p.o. administration. The relevance of this non-clinical observation with a different route of administration to humans is unknown.
There has been no carcinogenicity studies conducted with pseudoephedrine in combination with cetirizine.

The combination cetirizine/pseudoephedrine is neither mutagenic nor clastogenic and therefore unlikely to present a carcinogenic risk for humans. Cetirizine did not have any carcinogenic potential in rats and mice when dosed up to maximum tolerated dose (23 and 2.3 times the highest recommended daily dose in man, based on body surface area). No carcinogenicity study was performed with pseudoephedrine. However conventional carcinogenicity studies in mice and rats with the diastereomer ephedrine were concluded negative. Although there is a lack of carcinogenicity studies performed with combination cetirizine and pseudoephedrine, the combination was found neither mutagenic nor clastogenic and therefore unlikely to present a carcinogenic risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

- Hypromellose
- Microcrystalline cellulose
- Colloidal silica anhydrous
- Magnesium stearate
- Lactose monohydrate
- Croscarmellose sodium

Coating material:
Opadry Y-1-7000 which consists of:

- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 tablets are packed in thermoformed blisters (polyvinylchloride - aluminium)
6 or 14 tablets per blister; 1 blister per box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

UCB Pharma (Ireland) Ltd
United Drug House
Magna Drive
Magna Business Park
Citywest Road
Dublin 24
Ireland

8. MARKETING AUTHORIZATION NUMBER

PA0891/008/001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorisation: 30-Jun-2006
Date of latest renewal: 15-Sep-2010

10. DATE OF REVISION OF THE TEXT

05/2019