Summary of Product Characteristics

1. Name of the medicinal product

Remiflu Tablets Levocetirizine Dihydrochloride, Phenylephrine Hydrochloride & Paracetamol Tablets (2.5+10+500) mg

2. Qualitative and quantitative composition

Each tablet contains:
Levocetirizine DihydrochlorideUSP……2.5mg
Phenylephrine Hydrochloride Ph. Eur…10mg
Paracetamol Ph. Eur……500mg

3. Pharmaceutical form

White to off white, capsule shaped biconvex, uncoated tablets, plain on both side.

4. Clinical particulars

4.1 Therapeutic indications

Remiflu tablets are indicated for the symptomatic treatment of allergic rhinitis and common cold associated with fever and nasal congestion.

4.2 Posology and method of administration

Do not exceed the recommended daily dose.
The usual dosage is one tablet twice daily.

Dosage in renal impairment

Levocetirizine is known to be substantially excreted by the kidneys and the risk of advers reactions to this drug may be greater in patients with impaired renal function. Care should be taken in dose selection and it may be useful to monitor renal function.Dose adjustment for patients with renal impairment is as follows: • Mild renal impairment (creatinine clearance [CL] = 50- CR 80 mL/min): One tablet once daily is recommended;
• Moderate renal impairment (CL = 30-50 mL/min): One CR tablet once every other day is recommended;

4.3 Contraindications

Remiflu tablets are contraindicated in:

- Patients with hypersensitivity to levocetirizine or cetirizine, phenylephrine or othe sympathomimetics, paracetamol, to any of the excipients, to hydroxyzine or to any piperazine derivatives
- Patients with severe renal impairment or end stage renal disease at less than 10 ml/min creatinine clearance
- Patients on hemodialysis
- Patients with hepatic impairment
- Patients with diabetes, hyperthyroidism, hypertension,ventricular tachycardia and heart disease
- Phaeochromocytoma
- Closed angle glaucoma
- Patients taking tricyclic antidepressants, or beta blocking drugs and those who are taking or who have taken within the last two weeks monoamine oxidase inhibitors
- Concomitant use of other sympathomimetics (such as decongestants, appet i te suppressants and amphetamine-like psychostimulants).

4.4 Special warnings and precautions for use

Do not exceed the recommended dosage. Do not use with any other products containing paracetamol or decongestants.

Levocetirizine

Somnolence - The occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with levocetirizine. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination such as operating machinery or driving a motor vehicle after ingestion of Remiflu tablets. Concurrent use of Remiflu tablets with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

Urinary retention - Urinary retention has been reported with levocetirizine. The drug should be used with caution in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

Discontinue Remiflu tablets if urinary retention occurs.

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

Renal impairment - Levocetirizine is known to cause renal function impairment; increased risk of adverse reactions, hence dosage adjustment may be required.

Phenylephrine
Sympathomimetic amines should be used with caution in patients with bronchial asthma, thyroid disease, peripheral vascular disease or prostatic hypertrophy. **Paracetamol**
Immediate medical advice should be sought in the event of an overdose, even if the patient seems well, because of the risk of delayed serious liver damage. Since chronic, excessive consumption of alcohol may increase the risk of paracetamol induced hepatotoxicity, chronicalcoholics should be cautioned to avoid regular or excessive use of paracetamol, or alternatively to avoid chronic ingestion of alcohol. Clinicians should be consulted by patients who generally consume 3 or more alcoholcontaining drinks per day since paracetamol may increase the risk of hepatotoxicity. A safe dose for a chronic alcohol abuser has not been determined. Caution chronic alcoholics to limit paracetamol intake to <2g/day. If a rare sensitivity reaction occurs, the drug should be discontinued. The hazards of overdose are greater in those with (noncirrhotic) alcoholic liver disease.
Paracetamol should be used with caution in patients with preexisting anemia, since cyanosis may not be apparent despite dangerously high blood concentrations of methemoglobin. Although psychologic dependence on paracetamol may occur, tolerance and physical dependence do not appear to develop even with prolonged use.
Caution is recommended when giving paracetamol to patients with renal impairment. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients with dialysis.

Usage in pregnancy and lactation
Because of potential promotion of uterine contractility and peripheral vasoconstriction, with the possibility of fetal hypoxia due to phenylephrine, the drug is best avoided during pregnancy.
Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk, use in nursing mothers is not recommended.

Usage in paediatrics
Remiflu tablets are not recommended in children.

Usage in geriatrics
A reduction in the dosing may be necessary in the elderly patients. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased

hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Levocetirizine
In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No *in vivo* drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with raceme cetirizine.
Antipyrine, azithromycin, cimetidine, erythromycin an pseudoephedrine: Pharmacokinetic interaction studie performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine erythromycin, azithromycin and cimetidine.
Theophylline: A small decrease in the clearance of cetirizine was caused by concomitant administration of theophylline. It Is possible that higher theophylline doses could have a greater effect.
Ritonavir: Ritonavir increases the plasma AUC of cetirizine accompanied by an increase in half-life and a decrease in clearance of cetirizine. The disposition of ritonavir is not altered by concomitant cetirizine administration.
Ketoconazole: Prolongation of QT interval was observed following concomitant administration with cetirizine. No other clinically important interactions were reported following such concomitant use. Not considered clinically important.
CNS depressants or alcohol: In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.
Phenylephrine
Phenylephrine should be used with caution in combination with the following drugs as interactions have been reported. Monoamine oxidase inhibitors (including moclobemide): Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors.
Sympathomimetic amines: Concomi tant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.

Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa): Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased. Tricyclic antidepressants (e.g. amitriptyline): May increase the risk of cardiovascular side effects with phenylephrine.
Ergot alkaloids (ergotamine and methylsergide): Increased risk of ergotism.
Digoxin and cardiac glycosides: Increase the risk of irregular heartbeat or heart attack. **Paracetamol**
Anticonvulsants: Anticonvulsants (including phenytoin, barbiturates, carbamazepine), that induce hepatic microsomal enzymes may increase paracetamol-induced liver toxicity. **Aspirin:** Limited data indicate that administration of paracetamol does not inhibit the antiplatelet effect of aspirin.
Isoniazid: Concomitant administration of isoniazid with paracetamol may result in an increased risk of hepatotoxicity, but the exact mechanism of this interaction has not been established.
Oral anticoagulants: Since concomitant administration of paracetamol (especially when administered in high dosages or for prolonged periods) with oral anticoagulants may potentiate the effects of the oral anticoagulant, additional monitoring of prothrombin time (PT)/international normalized ratio (INR) values has been suggested for patients receiving oral anticoagulants following initiation of, or during sustained therapy with, large doses of paracetamol. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol; with increased risk of bleeding; occasional doses have no significant effect.
Anticholinergics: The onset of paracetamol effect may be delayed or decreased slightly when it is given concomitantly with anticholinergics, but the ultimate pharmacologic effect is not significantly affected by anticholinergics.
Propranolol: Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of paracetamol. Therefore, the pharmacologic effects of paracetamol may be increased.
Contraceptives: With oral contraceptives, there is increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of paracetamol.
Probenecid: Probenecid may increase the therapeutic effectiveness of paracetamol
Slightly
Lamotrigine: When given concomitantly with lamotrigine, serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects.

Loop diuretics: The effects of the loop diuretic may be decreased because paracetamol may decrease renal prostaglandin excretion and decrease plasma renin activity.
Cholestyramine: Cholestyramine reduces the absorption of paracetamol if given within one hour of paracetamol administration.
Zidovudine: The pharmacologic effects of zidovudine may be decreased because of enhanced nonhepatic or renal clearance of zidovudine.
Phenothiazine: The possibility of severe hypothermia should be considered in patients receiving concomitant phenothiazine and antipyretic (e.g. paracetamol) therapy.
Rifampin and sulfinpyrazone: The potential hepatotoxicity of paracetamol may be increased by large doses or long-term administration of rifampin and sulfinpyrazone because of hepatic microsomal enzyme induction.
Therapeutic effect of paracetamol may also be decreased with sulfinpyrazone therapy.
Metoclopramide and domperidone: The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.
Tricyclic antidepressants: Patients who have taken tricyclic antidepressants may show diminished ability to metabolise large doses of paracetamol, the plasma half life of which can be prolonged.
Chloramphenicol: Increased plasma concentration of chloramphenicol.
Diflunisal: Concomitant administration of diflunisal with paracetamol produces an increase in plasma levels of paracetamol. Paracetamol had no effect on diflunisal plasma levels. Caution should be used with concomitant administration of diflunisal and paracetamol and patients should be monitored carefully.

4.6 Pregnancy and lactation

Usage in pregnancy and lactation
Because of potential promotion of uterine contractility and peripheral vasoconstriction, with the possibility of fetal hypoxia due to phenylephrine, the drug is best avoided during pregnancy.
Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk, use in nursing mothers is not recommended.

Usage in paediatrics
Remiflu tablets are not recommended in children.

Usage in geriatrics
A reduction in the dosing may be necessary in the elderly patients. Dose selection for an elderly patient should be cautious, usually starting at the

low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with this combination. 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. Patients should be advised not to drive or operate machinery if affected by dizziness.

4.8 Undesirable effects

Levocetirizine
The frequency of undesirable effects has been defined as: 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 system disorders: Very rare: Thrombocytopenia.
Cardiac disorders: *Rare:*Tachycardia.
Eye disorders: *Very rare:* Accomodation disorder, blurred vision, oculogyration.
Gastrointestinal disorders: *Common:* Abdominal pain, constipation, drymouth, nausea;
*Uncommon:*Diarrhoea
General disorders and administration site conditions:
Common: Fatigue; *Uncommon:* Asthenia, Malaise; *Rare:* Oedema.
Hepatobiliary disorders: *Rare:* Hepatic function abnormal (increased transaminases, alklaline phosphatise, !-GT and bilirubin), hepatitis.
Immune systemdisorders: *Rare:* Hypersensitivity; *Very rare:* Anaphylactic shock. **Investigations*:*** *Rare:*Weight increased.
Nervous system disorders: *Common:* Dizziness, headache;
Uncommon: Paraesthesia; *Rare:* Convulsions, movement disorders; *Very rare:* Dysgeusia, syncope, tremor, dystonia, dyskinesia.
Psychiatric disorders: *Common:* Somnolence; *Uncommon:*
Agitation; *Rare:* Aggression, confusion, depression,hallucination, insomnia; *Very rare:*Tic.

Respiratory, thoracic and mediastinal disorders: *Common:* Xerostomia, nasopharyngitis, pharyngitis
Renal and urinary disorders: *Very rare:* Dysuria,
Enuresis; *Not known:* Urinary retention.
Skin and subcutaneous tissue disorders: *uncommon:* Pruritus, Rash; *Rare:* Urticaria; *Very rare:* Angioneurotic oedema, fixed drug eruption. Other adverse events reported include vertigo, increased appetite, suicidal ideation, visual disturbance, palpitation, dyspnea and myalgia. Since levocetirizine is the principal pharmacologically active component of cetirizine, one should take into account the fact that the following adverse events which have been reported with cetirizine could also potentially occur under treatment with levocetirizine:
orofacial dyskinesia, severe hypotension, cholestasis, glomerulonephritis, and still birth.
Phenylephrine
The following adverse events represent the most commonly occurring adverse events with phenylephrine.
Cardiac disorders: Increased blood pressure.
Gastrointestinal disorders: Nausea, Vomiting.
Nervous system disorders: Headache, dizziness, insomnia, anxiety, convulsions, hallucinations.
Psychiatric disorders: Nervousness, irritability, restlessness,
Following adverse reactions have been reported with
phenylephrine. The frequency of these reactions is unknown but likely to be rare.
Cardiac disorders:Tachycardia, palpitations.
Eye disorders: Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma.
Renal and urinary disorders: Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy. Skin and subcutaneous disorders: Allergic reactions (e.g. rash, urticaria, allergic dermatitis).
Hypersensitivity reactions –including that cross-sensitivity may
occur with other sympathomimetics. **Paracetamol**
Paracetamol is relatively non-toxic in therapeutic doses.
Following adverse effects may occur:
Dermatologic and sensitivity reactions – Dermatologic reactions including pruritic maculopapular rash, and urticaria have been reported and other sensitivity reactions including laryngeal edema, angioedema, and anaphylactoid reactions may occur rarely. **Hematologic effects** - Thrombocytopenia, leukopenia, and pancytopenia have been associated with the use of paminophenol derivatives, especially with prolonged administration of large dose. Neutropenia methaemoglobenaemia and

thrombocytopenic purpura have been reported with paracetamol use. Rarely agranulocytosis has been reported in patients receiving paracetamol.
Hepatic effects - Hepatotoxicity can result from ingestion of single toxic dose or multiple excessive doses of paracetamol.
Renal - Cases of renal damage (without hepatic damage) have been reported.
Miscel laneous - Hypoglycemic coma, jaundice. Nephrotoxicity following therapeutic doses of paracetamol is uncommon, but papillary necrosis has been reported after prolonged administration. **Laboratory tests**
Paracetamol in therapeutic doses may interfere with the determination of 5-hydroxycindoleacetic acid (5HIAA), causing false positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Levocetirizine
Symptoms observed after an overdose of levocetirizine 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.
There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence. Levocetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested.

Phenylephrine
Phenylephrine overdosage is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include hypertension and possibly reflux bradycardia. In severe cases confusion, hallucinations, seizures and arrythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than required to cause paracetamol-related toxicity.

The treatment of overdosage should provide symptomatic and supportive care. If the amount ingested is considered dangerous or excessive, induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage using a large-bore tube. If indicated, follow with activated charcoal and a saline cathartic. Severe hypertension may need to be treated with an alpha blocking drug such as phentolamine. **Paracetamol**
Paracetamol in massive overdosage may cause hepatic toxicity in some patients. In adults and adolescents (> 12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams over a period of 8 hours or less.
Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. Early symptoms following a potentially hepatotoxic overdose may include nausea, vomiting, diaphoresis and general malaise.
Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage,
hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.
Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post ingestion. If required the patient should be given intravenous-Nacetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. The additional procedure recommended is to promptly initiate gastric decontamination of the stomach.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Levocetirizine
Levocetirizine, the active enantiomer of cetirizine, is a second generation antihistamine;
its principal effects are mediated via selective inhibition of H receptors binding studies 1 *In vitro* revealed that levocetirizine has an affinity for the human H –
1 receptor 2-fold higher than that of cetirizine (Ki = 3 nmol/L vs. 6 nmol/L, respectively). The clinical relevance of this finding is unknown.
Phenylephrine
Phenylephrine is a sympathomimetic agent with mainly direct effects on adrenergic receptors (predominantly alphaadrenergic activity) and provides relief from nasal congestion due to its vasoconstrictor action. **Paracetamol**
Paracetamol is a clinically proven analgesic/antipyretic. Paracetamol produce analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat regulating center. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system and to a lesser extent, through a peripheral action by blocking pain impulse generation. Paracetamol produces antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. Paracetamol is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirincontaining products. Paracetamol does not inhibit platelet aggregation, affect prothrombin response or produce GI ulceration.

5.2 Pharmacokinetic properties

Levocetirizine
Levocetirizine is rapidly and extensively absorbed following oral administration. The extent of absorption is not altered by food, but the peak concentration is reduced and delayed. The mean plasma protein binding of levocetirizine *in vitro* ranged from 91 to 92%, The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of hepatic drug metabolizing enzyme inhibitors are expected to be negligible. The plasma half-life is about 8 to 9 hours. The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose.
Excretion via feces accounts for only 12.9% of the dose. In patients with renal impairment the clearance of levocetirizine is reduced.
Phenylephrine
Due to irregular absorption and first pass metabolism by monoamine oxidase in the gut and liver, phenylephrine has reduced bioavailability from

the gastrointestinal tract. It undergoes extensive biotransformation in the intestinal wall during absorption.
Following absorption, the drug is extensively biotransformed in the liver. The principal routes of metabolism are to sulphate conjugates, which are formed largely in the gut wall, and oxidative deamination by monoamine oxidase. It is excreted in the urine almost entirely as the sulphate conjugate.

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the GI tract following oral administration. Following oral administration, peak plasma concentrations are achieved within 30-60 minutes. Paracetamol is rapidly and uniformly distributed into most body tissues. About 25% of paracetamol in blood is bound to plasma proteins.
About 80-85% of the paracetamol in the body undergoes conjugation principally with glucuronic acid and to lesser extent with sulfuric acid. Paracetamol is also metabolized by microsomal enzyme systems in the liver. Paracetamol is excreted in urine principally as paracetamol glucuronide with small amounts of paracetamol sulfate and mercaptate and unchanged drug.Approximately 85% of a dose of paracetamol is excreted in urine as free and conjugated paracetamol within 24 hours after ingestion. It has an elimination half-life of 1.25 to 3 hours.
Administration of paracetamol to patients with moderate to severe renal impairment may result in accumulation of paracetamol conjugates

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1 List of excipeints

Pregelatinized starch BP/EP, Microcrystalline cellulose (102) BP/EP, Colloidal anhydrous silica BP/EP, Sodium starch glycollate (Type A) BP/EP, Magnesium stearate BP/EP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in a dry place.

Keep out of reach of children

6.5 Nature and contents of container

Foil Blister of 10 tablets, 1 such strip packed in a printed show box along with leaflet.

7. Marketing authorisation holder

Ipca Laboratories Limited

8. Marketing authorisation number(s)

H2022/CTD6495/12726

9. Date of first authorisation/renewal of the authorisation

17/02/2023

10. Date of revision of the text

17/02/2023