1. Name of the medicinal product

Paracetamol, Chlorphenamine Maleate,Phenylepherine & Menthol Tablets (Royalkel Tablets)

2. Qualitative and quantitative composition

Each Uncoated tablet contains:
Paracetamol B.P……..…500 mg
Chlorphenamine Maleate B.P……..2.0mg
Phenylepherine HCL B.P……....2.5mg
Menthol B.P……..…….….0.75mg

3. Pharmaceutical form

Uncoated tablet
Pink colour, round, flat,one side marks "C+L" and other side break line uncoated tablet

4. Clinical particulars

4.1 Therapeutic indications

Royalkel is indicated for the relief of symptoms associated with colds and influenza such as nasal congestion , headache, aches and pains and fever.

4.2 Posology and method of administration

Posology: Dosing based on patient weight (please see the dosing table here below)

Patient weight	Dose per administration	Volume per administration	Maximum volume of Paracetamol Baxter (10 mg/mL) per administration based on upper weight limits of group (mL)**	Maximum Daily Dose *
> 33 kg to ≤50kg	15 mg/kg	1.5mL/kg	75 mL	60mg/kg not exceeding 3g
>50 kg with additional risk factors for hepatotoxicity	1g	100mL	100mL	3g
> 50 kg and no additional risk factors for hepatotoxicity	1g	100mL	100mL	4g

* **Maximum daily dose:** The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted accordingly taking such products into account.

** Patients weighing less will require smaller volumes.

The minimum interval between each administration must be at least 4 hours. No more than 4 doses to be given in 24 hours**.**

The minimum interval between each administration in patients with severe renal impairment must be at least 6 hours.

Renal impairment:

In patients with renal impairment, the minimum interval between each administration should be modified according to the following schedule:

Creatinine clearance	Dosing interval
≥50 mL/min	4 hours
10-50 mL/min	6 hours
<10 mL/min	8 hours

Hepatic insufficiency

In patients with chronic or compensated active hepatic disease, hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration, Gilbert's syndrome, weighing less than 50 kg: The maximum daily dose must not exceed 3 g

Elderly Patients

No dose adjustment is usually required in geriatric patients.

Method of administration:

Orally administered

4.3 Contraindications
It is contraindicated to patients with known hypertention and severe or unstable ishemic heart disease. It is also contraindicated in concurrent use of monoamine oxidase inhibitor, prostatic hypertrophy or urinary retention, intestinal obstruction, severe hyperthyroidism and glucoma.

4.4 Special warnings and precautions for use
Warnings

It may cause drowsiness, dizziness, dry mouth/nose/throat, headache, upset stomach, constipation, or trouble sleeping may occur. If any of these effects last or get worse, tell your doctor or pharmacist promptly.

If your doctor has directed you to use this product, remember that your doctor has judged that the benefit to you is greater than the risk of side effects. Many people using this product do not have serious side effects.

Tell your doctor right away if you have any serious side effects, including: mental/mood changes (such as confusion, hallucinations), ringing in the ears, difficulty urinating, vision changes (such as blurred/double vision).

Get medical help right away if you have any very serious side effects, including: fast/irregular heartbeat, seizure.

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

Precautions for use
Before taking this product, tell your doctor or pharmacist if you are allergic to any of its ingredients; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: breathing problems (such as asthma, emphysema), diabetes, glaucoma, heart problems, high blood pressure, kidney problems, liver disease, seizures, stomach/intestinal problems (such as ulcers, blockage), overactive thyroid (hyperthyroidism), difficulty urinating (such as due to enlarged prostate).

This drug may make you dizzy or drowsy. Alcohol or marijuana (cannabis) can make you more dizzy or drowsy. Do not drive, use machinery, or do anything that needs alertness until you can do it safely. Limit alcoholic beverages. Talk to your doctor if you are using marijuana (cannabis).

Liquid products, chewable tablets, or dissolving tablets/strips may contain sugar or aspartame. Liquid products may also contain alcohol. Caution is advised if you have diabetes, alcohol dependence, liver disease, phenylketonuria (PKU), or any other condition that requires you to limit/avoid these substances in your diet. Ask your doctor or pharmacist about using this product safely.

Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).

Children may be more sensitive to the side effects of this product, especially excitation and agitation.

Older adults may be more sensitive to the side effects of this product, especially dizziness, drowsiness, confusion, constipation, fast/irregular heartbeat, trouble sleeping, or urination problems. Dizziness, drowsiness, trouble sleeping, and confusion can increase the risk of falling.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interaction may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use (including prescription/nonprescription drugs and herbal products) and share it with your doctor and pharmacist. Do not start, stop, or change the dosage of any medicines without your doctor's approval.

Some products that may interact with this drug are: antihistamines applied to the skin (such as diphenhydramine cream, ointment, spray), blood pressure medications (especially guanethidine, methyldopa, beta blockers such as atenolol, or calcium channel blockers such as nifedipine).

Taking MAO inhibitors with this medication may cause a serious (possibly fatal) drug interaction. Avoid taking MAO inhibitors (isocarboxazid, linezolid, metaxalone, methylene blue, moclobemide, phenelzine, procarbazine, rasagiline, safinamide, selegiline, tranylcypromine) during treatment with this medication. Most MAO inhibitors should also not be taken for two weeks before treatment with this medication. Ask your doctor when to start or stop taking this medication.

Tell your doctor or pharmacist if you are taking other products that cause drowsiness such as opioid pain or cough relievers (such as codeine, hydrocodone), alcohol, marijuana (cannabis), drugs for sleep or anxiety (such as alprazolam, lorazepam, zolpidem), muscle relaxants (such as carisoprodol, cyclobenzaprine), or other antihistamines (such as cetirizine, diphenhydramine).

Check the labels on all your medicines (such as allergy or cough-and-cold products, diet aids) because they may contain ingredients that could affect your blood pressure or cause drowsiness. Ask your pharmacist about using those products safely.

This medication may interfere with certain medical/lab tests (such as brain scan for Parkinson's disease, urine drug screening tests), possibly causing false test results. Make sure lab personnel and all your doctors know you use this drug.

4.6 Fertility, pregnancy and lactation

During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor.

This medication may pass into breast milk and the effect on a nursing infant is unknown. Consult your doctor before breast-feeding.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
It generally well tolerated and undesirable effectsc are rare. Hypersensitive individuals may display ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness and nausea. Use of sympathomimetics has been associated with fear, anxiety, restlessness, tremor, weakness, dysuria, insomnia, hallucinations and convulsions. Chlorpheniramine in may cause sedation.

4.9 Overdose

Symptoms of overdose may include: irregular heartbeat, hallucinations, fainting, seizures, dry mouth, large pupils, flushing, nausea, vomiting, abdominal pain, diarrhoea and sweating.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Paracetamol is a widely used analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics. It is extremely safe in standard doses, but because of its wide availability, deliberate or accidental overdoses are not uncommon. Paracetamol, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties or effects on platelet function, and it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs. At therapeutic doses Paracetamol does not irritate the lining of the stomach nor affect blood coagulation, kidney function, or the fetal ductus arteriosus (as NSAIDs can). Like NSAIDs and unlike opioid analgesics, Paracetamol does not cause euphoria or alter mood in any way. Paracetamol and NSAIDs have the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal. Paracetamol is used on its own or in combination with pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, doxylamine, codeine, hydrocodone, or oxycodone. Phenylephrine is a powerful vasoconstrictor. It is used as a nasal decongestant and cardiotonic agent. Phenylephrine is a postsynaptic α1-receptor agonist with little effect on βreceptors of the heart. Parenteral administration of phenylephrine causes a rise in systolic and diastolic pressures, a slight decrease in cardiac output, and a considerable increase in peripheral resistance; most vascular beds are constricted, and renal, splanchnic, cutaneous, and limb blood flows are reduced while coronary blood flow is increased. Phenelephrine also causes pulmonary vessel constriction and subsequent increase in pulmonary arterial pressure. Vasoconstriction in the mucosa of the respiratory tract leads to decreased edema and increased drainage of sinus cavities. Chlorpheniramine maleate is a histamine H1 antagonist of the alkylamine class. It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and

respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.

Mechanism of Action: Paracetamol act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. The antipyretic properties of acetaminophen are likely due to direct effects on the heat-regulating centres of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation. Phenylephrine decreases nasal congestion by acting on α1-adrenergic receptors in the arterioles of the nasal mucosa to produce constriction; this leads to decreased edema and increased drainage of the sinus cavities. In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine maleate binds to the histamine H1 receptor. This block the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours. Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (Nacetyl-p-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol over dosage and cause tissue damage. Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscularly it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about 1 hour and up to about 2 hours, respectively. Intravenous injections are effective for about 20 minutes. Systemic absorption follows topical application. Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide inter individual variation in the pharmacokinetics of chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS. Chlorphenamine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces. Duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters. More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of paracetamol in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. Pharmaceutical particulars

6.1 List of excipients

Micro Crystalline Cellulose pH-101, Starch, Methyl Paraben Sodium, Propyl Paraben Sodium, PVPK-30, Colour Erythrosine (Supra), Sod. Starch Glycolate, Mag. Stearate, Talcum Purified and aerosil

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal product.

6.3 Shelf life

3 years from the manufacturing date

6.4 Special precautions for storage

Do not refrigerate or freeze. Store below 30 °C in a dark and dry place

6.5 Nature and contents of container

100x10x10 Tabs

6.6 Special precautions for disposal and other handling

No special requirements.