

## SUMMARY OF PRODUCT CHARACTERISTICS (ColdReief™ Forte Effervescent)

### 1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ColdReief™ Forte Effervescent

Paracetamol 500 mg, Phenylephrine Hydrochloride 10 mg, and Chlorpheniramine Maleate 2 mg Effervescent Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### 2.1 Active Ingredients

Each effervescent tablet contains:

Active Ingredient	Quantity	Form
Paracetamol (INN)	500 mg	USP/BP Grade
Phenylephrine Hydrochloride (INN)	10 mg	USP/BP Grade
Chlorpheniramine Maleate (INN)	2 mg	USP/BP Grade

For full list of excipients, see section 6.1

### 3. PHARMACEUTICAL FORM

#### Effervescent Tablet

**Appearance:** Round, flat, yellow-colored effervescent tablet with embossed "CR-12" on one side

**Diameter:** 17 mm

**Thickness:** 6 mm

**Average Weight:** 2.0 g per tablet

**Description:** ColdReief™ Forte Effervescent is an off-white to pale yellow colored, round effervescent tablet with a characteristic sharp lemon odor. The tablet dissolves rapidly in water at room temperature, releasing carbon dioxide gas and producing an effervescent solution suitable for oral administration.

**Route of Administration:** Oral

**Dissolution Time:** 3-5 minutes in 200 mL water at 20-25°C

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

ColdReief™ Forte Effervescent is indicated for the symptomatic relief of:

- Fever associated with common cold and flu-like symptoms
- Nasal congestion and stuffiness
- Headache and body aches
- Sore throat pain
- Sneezing and watery eyes associated with allergic rhinitis
- Minor muscular and joint pain

This product is indicated for the short-term symptomatic treatment of common cold and flu-like illnesses in adult patients. The product provides combined analgesic, antipyretic, decongestant, and antihistaminic benefits through its fixed-dose combination formulation.

#### 4.2 Posology and Method of Administration

**Dosage in Adults (≥18 years):**

**Recommended Dose:** 1 tablet (containing 500 mg Paracetamol, 10 mg Phenylephrine HCl, and 2 mg Chlorpheniramine Maleate)

**Frequency:** Every 4-6 hours as needed for symptom relief

**Maximum Daily Dose:** 4 tablets per 24 hours

**Duration of Use:** Do not use continuously for more than 7 days without consulting a healthcare professional

**Dosage in Geriatric Patients (>65 years):**

**Recommended Dose:** 1 tablet every 6-8 hours

**Maximum Daily Dose:** 3 tablets per 24 hours

**Special Precaution:** Use with caution in elderly patients due to increased sensitivity to anticholinergic effects and potential drug interactions

**Not Recommended Populations:**

- Children under 12 years of age
- Pregnant women (especially third trimester)
- Nursing mothers
- Patients with severe hepatic or renal impairment

**Method of Administration:**

1. Dissolve 1 tablet in a glass of water (approximately 200 mL) at room temperature
2. Stir well for 30 seconds to ensure complete dissolution
3. Drink the resulting solution immediately while fizzing
4. Do not exceed recommended dosage
5. Do not take without food or with alcohol
6. Allow at least 4-6 hours between consecutive doses

**Note:** The effervescent formulation increases gastric pH and accelerates absorption compared to standard tablets, potentially providing faster onset of action (approximately 15-20 minutes).

**4.3 Contraindications**

ColdReief™ Forte Effervescent is contraindicated in patients with:

- Known hypersensitivity to paracetamol, phenylephrine, chlorpheniramine maleate, or any excipients listed in section 6.1
- Severe hepatic impairment (Child-Pugh score C) or active liver disease
- Severe renal impairment (eGFR <15 mL/min/1.73m<sup>2</sup>)
- Uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg)
- Coronary artery disease, myocardial infarction (within 6 months), or angina pectoris
- Pheochromocytoma
- Narrow-angle glaucoma
- Severe cardiovascular disease
- Concurrent use with monoamine oxidase (MAO) inhibitors within 14 days
- Acute intermittent porphyria
- Phenylketonuria (due to aspartame content)
- Hyperthyroidism or thyroid disorders requiring treatment
- Patients receiving triple reuptake inhibitors or certain antidepressants with sympathomimetic interactions

**4.4 Special Warnings and Precautions for Use**

**Warnings:**

**Hepatotoxicity Risk:**

Paracetamol can cause serious hepatotoxicity. Risk is increased in patients with:

- Chronic alcohol consumption (≥3 drinks daily)
- Pre-existing liver disease or hepatitis
- Malnutrition
- Dehydration
- Simultaneous use of other paracetamol-containing products

Maximum daily paracetamol dose should not exceed 3000-4000 mg in adults. Patients should be warned to check all medications for paracetamol content before using ColdReief™ Forte.

**Cardiovascular Precautions:**

Phenylephrine has sympathomimetic properties and may cause:

- Increased blood pressure
- Tachycardia

- Palpitations
- Tremor
- Anxiety

Use with caution in patients with:

- Mild to moderate hypertension (BP 140-179/90-109 mmHg) - dose adjustment may be required
- Type 2 Diabetes Mellitus
- Hyperthyroidism (subclinical)
- Cardiac arrhythmias
- History of cerebrovascular accident
- Prostatic hypertrophy with urinary retention symptoms

#### Anticholinergic Effects:

Chlorpheniramine may cause anticholinergic effects including:

- Drowsiness and impaired cognitive function
- Dry mouth
- Urinary retention
- Constipation
- Tachycardia
- Increased intraocular pressure (relevant for glaucoma patients)

#### Sodium Content:

Each tablet contains approximately 320 mg sodium (from sodium bicarbonate and sodium carbonate), equivalent to 14% of the EU recommended daily intake. Patients on sodium-restricted diets should use with caution.

#### Precautions:

- **Driving and Machine Operation:** Chlorpheniramine may cause drowsiness. Patients should not drive or operate heavy machinery until they know how this medication affects them.
- **Alcohol Interaction:** Concurrent consumption of alcohol significantly increases hepatotoxicity risk and enhances CNS depression. Absolute avoidance is recommended.
- **Pregnancy:** Paracetamol is generally considered safe in pregnancy. Phenylephrine should be avoided, especially in the third trimester due to potential vasoconstriction effects on placental blood flow. Chlorpheniramine should be avoided, particularly in early pregnancy.
- **Lactation:** Paracetamol and chlorpheniramine appear in breast milk in small quantities. Phenylephrine passage in breast milk is not well-studied. Risk-benefit analysis required; alternative feeding methods should be considered.
- **Renal Impairment:** Dose adjustment required in moderate renal impairment (eGFR 30-59 mL/min/1.73m<sup>2</sup>). Maximum daily dose should be reduced to 3 tablets per 24 hours.
- **Hepatic Impairment:** Avoid in moderate to severe impairment. In mild impairment, maximum daily dose should not exceed 3 tablets per 24 hours.
- **G6PD Deficiency:** Phenylephrine may theoretically pose a risk in G6PD-deficient patients; clinical significance is unclear but caution is advised.
- **Bronchial Asthma:** Antihistamines may have variable effects; use with caution and monitor.

#### 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

##### Major Drug Interactions:

Drug Class	Specific Drug/Examples	Interaction Mechanism	Clinical Significance	Management
<b>Monoamine Oxidase Inhibitors</b>	Tranlycypromine, Phenelzine, Isocarboxazid	Phenylephrine is sympathomimetic; concurrent use increases hypertensive crisis risk	<b>MAJOR</b> - Contraindicated	Contraindicated within 14 days of MAO inhibitor use; allow 14-day washout

<b>Tricyclic Antidepressants</b>	Amitriptyline, Nortriptyline, Imipramine	Potential of sympathomimetic effects; increased BP and heart rate	<b>MAJOR</b>	Avoid concurrent use or monitor BP closely; consider alternative antidepressant
<b>Serotonin-Norepinephrine Reuptake Inhibitors</b>	Venlafaxine, Duloxetine	Increased sympathomimetic effects; hypertensive crisis possible	<b>MAJOR</b>	Use with caution; monitor blood pressure and heart rate; educate patient on warning signs
<b>Sympathomimetic Agents</b>	Ephedrine, Pseudoephedrine, Decongestants	Additive sympathomimetic effects	<b>MAJOR</b>	Avoid concurrent use; ensure patient does not take other decongestants
<b>Warfarin and Anticoagulants</b>	Warfarin, Apixaban, Rivaroxaban	High-dose paracetamol (>2 g/day) increases INR/anticoagulant effect	<b>MODERATE</b>	Monitor INR; limit paracetamol to ≤2 g/day; advise patient
<b>First-Generation Antihistamines</b>	Diphenhydramine, Promethazine, Cetirizine	Additive anticholinergic and CNS depressant effects	<b>MAJOR</b>	Avoid concurrent use; assess need for antihistamine combination
<b>Alcohol (Ethanol)</b>	All alcohol-containing beverages	Increased hepatotoxicity risk with paracetamol; enhanced CNS depression with chlorpheniramine	<b>MAJOR</b>	Absolute contraindication; strong patient education required
<b>Methotrexate</b>	Methotrexate	Paracetamol may reduce methotrexate elimination; increased toxicity risk	<b>MODERATE</b>	Use alternative analgesic/antipyretic; monitor if absolutely necessary
<b>Chlorpromazine and Phenothiazines</b>	Chlorpromazine, Promethazine	Additive anticholinergic effects; risk of severe antimuscarinic syndrome	<b>MAJOR</b>	Avoid concurrent use; consider alternative antipsychotic or pain reliever
<b>Beta-blockers</b>	Propranolol, Atenolol, Metoprolol	Phenylephrine may reduce efficacy; potential for severe hypertension breakthrough	<b>MODERATE</b>	Monitor BP; may need beta-blocker dose adjustment
<b>Antihypertensive Medications</b>	ACE inhibitors, ARBs, Calcium channel blockers	Phenylephrine counteracts antihypertensive effects	<b>MAJOR</b>	Monitor BP closely; advise patient on phenylephrine's hypertensive effects
<b>Anticholinergic Agents</b>	Atropine, Benztropine, Trihexyphenidyl	Chlorpheniramine has anticholinergic properties; additive effects	<b>MAJOR</b>	Avoid concurrent use; assess necessity of both agents
<b>Oral Hypoglycemic Agents</b>	Metformin, Sulfonylureas, SGLT2 inhibitors	Phenylephrine may cause hyperglycemia; counteracts hypoglycemic effect	<b>MODERATE</b>	Monitor blood glucose; may require dose adjustment of antidiabetic agent
<b>Paroxetine and Other SSRIs</b>	Paroxetine (in high doses)	Potential for anticholinergic effects accumulation	<b>MINOR</b>	Monitor; generally acceptable with caution

#### Moderate Drug Interactions:

- **Paracetamol + Barbiturates (Phenobarbital, Butobarbital):** Barbiturates induce hepatic metabolism of paracetamol, potentially increasing risk of hepatotoxic metabolites; avoid concurrent chronic use
- **Paracetamol + Isoniazid:** Increased hepatotoxicity risk; avoid if possible or monitor liver function tests
- **Paracetamol + Zidovudine:** May increase risk of hematologic toxicity and hepatotoxicity
- **Chlorpheniramine + Opioids (Morphine, Codeine, Oxycodone):** Additive CNS depression; increased sedation, respiratory depression risk; use together cautiously with dose adjustment
- **Chlorpheniramine + Benzodiazepines:** Enhanced CNS depression; caution with concurrent use; dose adjustments may be required
- **Chlorpheniramine + Sedating Antidepressants:** Cumulative CNS depression; use alternative antidepressant if possible
- **Phenylephrine + NSAIDs:** May increase cardiovascular risk and hypertension; concurrent use should be monitored
- **Phenylephrine + Decongestants (Oral Formulations):** Additive sympathomimetic effects; avoid concurrent use
- **Paracetamol + Other Paracetamol-containing Products:** Risk of overdose and hepatotoxicity; total daily paracetamol must not exceed 3000-4000 mg; patient education essential

**Food and Herbal Interactions:**

- **Alcohol:** Significantly increases hepatotoxicity risk with paracetamol; absolute contraindication
- **Caffeine:** Products containing caffeine may potentiate sympathomimetic effects of phenylephrine; advise limiting caffeine intake
- **St. John's Wort:** May induce metabolism of phenylephrine; potential loss of efficacy
- **Ma Huang (Ephedra):** Contains ephedrine; concurrent use increases sympathomimetic effects and hypertensive crisis risk; contraindicated
- **Ginseng:** May potentiate sympathomimetic effects; advised against concurrent use
- **Yohimbine:** Potentiates sympathomimetic effects; avoid concurrent use

**4.6 Fertility, Pregnancy and Lactation****Pregnancy (Category B/C mixed):**

**Paracetamol:** Category B - Generally considered safe during all trimesters. Extensive clinical data supports safety. Maximum recommended dose should not be exceeded.

**Phenylephrine:** Category C - Limited human data. Animal studies have not demonstrated fetal risk, but potential concerns exist regarding placental vasoconstriction. Should be avoided, especially in third trimester. Risk of intrauterine growth restriction reported in some studies.

**Chlorpheniramine:** Category B - Generally considered safe, but some studies suggest increased risk of cleft palate in early pregnancy (first trimester). Avoid in early pregnancy if possible; acceptable in second and third trimesters.

**Recommendation:** ColdReief™ Forte Effervescent is NOT recommended for routine use during pregnancy. For pregnant women with common cold symptoms:

- Consider non-pharmacologic measures first (rest, fluids, saline rinse)
- Paracetamol monotherapy (500 mg) at regular intervals may be considered if benefit outweighs risk
- Phenylephrine and chlorpheniramine should be avoided
- Consultation with healthcare provider is strongly advised before use

**Lactation:**

**Paracetamol:** Appears in breast milk in small quantities (estimated <2% of maternal dose). Considered safe for breastfeeding mothers. Infant exposure unlikely to cause harm at recommended maternal doses.

**Phenylephrine:** Limited data on passage into breast milk. Use in nursing mothers is generally not recommended. If use is necessary, monitor infant for signs of sympathomimetic effects (agitation, poor feeding, tremor).

**Chlorpheniramine:** Appears in breast milk; estimated <5% of maternal dose. May cause drowsiness and poor feeding in susceptible infants. Use with caution in nursing mothers.

**Recommendation:** Breastfeeding mothers should consult healthcare provider before use. Alternative feeding methods (expressed breast milk) may be advisable if medication is deemed necessary.

**Fertility:**

No studies have demonstrated adverse effects on male or female fertility. Use of ColdReief™ Forte Effervescent is not expected to affect fertility. No special precautions are required for individuals planning conception.

#### 4.7 Effects on Ability to Drive and Operate Machinery

Chlorpheniramine may cause drowsiness, dizziness, and impaired cognitive function in some patients, particularly at higher doses or in susceptible individuals. These effects are more pronounced:

- During initial treatment (first 3-5 days)
- In elderly patients
- In patients with hepatic or renal impairment
- When combined with alcohol or other CNS depressants

**Patient Guidance:** Patients should be advised NOT to drive motor vehicles or operate hazardous machinery until they know how ColdReief™ Forte Effervescent affects them. The response may vary between individuals.

**Residual Effects:** Even morning-after drowsiness can impair driving ability. Patients taking evening doses should avoid driving the following day if drowsiness persists.

**Clinical Recommendation:** For patients whose occupation requires alertness (truck drivers, pilots, machinery operators), alternative medications or dose adjustment may be necessary.

#### 4.8 Undesirable Effects

##### Summary of Safety Profile:

Clinical trials and post-marketing surveillance have demonstrated that ColdReief™ Forte Effervescent is generally well-tolerated. The adverse event profile reflects the combined pharmacological effects of the three active ingredients. Common adverse events are typically mild to moderate and transient, resolving without discontinuation of medication.

**Overall Adverse Event Incidence:** Approximately 15-20% of patients report at least one adverse event during treatment course (typical duration: 3-7 days).

##### Adverse Events by System Organ Class:

###### Nervous System Disorders:

- **Very Common (≥10%):** Drowsiness, dizziness, headache
- **Common (1-10%):** Tremor, anxiety, nervousness, insomnia, restlessness
- **Uncommon (0.1-1%):** Seizures (rare, high-dose overdose), confusion, agitation
- **Rare (<0.1%):** Hallucinations, psychosis, encephalopathy (in hepatotoxicity cases)

###### Gastrointestinal Disorders:

- **Common (1-10%):** Nausea, vomiting, dry mouth, constipation, abdominal discomfort
- **Uncommon (0.1-1%):** Diarrhea, dyspepsia, gastritis
- **Rare (<0.1%):** Hepatotoxicity, acute liver failure (in overdose or with alcohol)

###### Cardiovascular Disorders:

- **Common (1-10%):** Palpitations, tachycardia, mild elevation in blood pressure
- **Uncommon (0.1-1%):** Hypertensive crisis, angina, myocardial infarction, arrhythmia
- **Rare (<0.1%):** Stroke, severe cardiac event (in susceptible patients)

###### Respiratory, Thoracic and Mediastinal Disorders:

- **Uncommon (0.1-1%):** Dyspnea, bronchospasm (in asthmatic patients)
- **Rare (<0.1%):** Acute respiratory distress (severe cases)

###### Skin and Subcutaneous Tissue Disorders:

- **Common (1-10%):** Rash, urticaria
- **Uncommon (0.1-1%):** Pruritus, erythema
- **Rare (<0.1%):** Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), anaphylaxis

###### Renal and Urinary Disorders:

- **Uncommon (0.1-1%):** Urinary retention, dysuria
- **Rare (<0.1%):** Acute kidney injury (in overdose cases)

###### General Disorders:

- **Common (1-10%):** Fatigue, weakness, malaise

- **Uncommon (0.1-1%):** Edema, fever (usually transient)

**Eye Disorders:**

- **Uncommon (0.1-1%):** Mydriasis, increased intraocular pressure, blurred vision
- **Rare (<0.1%):** Acute glaucoma attack (in susceptible patients)

**Immune System Disorders:**

- **Rare (<0.1%):** Anaphylaxis, angioedema, severe allergic reactions

**Additional Serious Adverse Events (Post-Marketing Surveillance):**

- Hepatotoxicity and acute liver failure (associated with overdose, chronic alcohol use, or pre-existing liver disease)
- Severe hypertensive episodes (particularly in patients with undiagnosed/uncontrolled hypertension)
- Myocardial infarction and acute coronary syndrome (in susceptible cardiovascular patients)
- Cerebrovascular accident/stroke (associated with severe hypertensive episodes)
- Severe cutaneous adverse reactions including SJS and TEN (very rare)
- Anaphylaxis and severe allergic reactions (rare, associated with hypersensitivity)

**Reporting of Suspected Adverse Reactions:**

Reporting suspected adverse reactions after authorization of the medicinal product is important as it allows continued monitoring of benefit/risk balance. Healthcare professionals and patients are encouraged to report any suspected adverse reactions via the national pharmacovigilance system (see contact details in Section 11 or local equivalent authority).

**4.9 Overdose****Signs and Symptoms:**

Overdose symptoms manifest based on the predominant active ingredient responsible:

**Paracetamol Overdose (Early Phase - 0-24 hours):**

- Nausea, vomiting, abdominal pain
- Anorexia
- Pallor
- Diaphoresis (sweating)
- General malaise
- Usually appears minor or absent

**Paracetamol Overdose (Hepatotoxic Phase - 24-72 hours):**

- Right upper quadrant (RUQ) pain and tenderness
- Jaundice
- Prothrombin time (PT) prolongation
- Hepatic transaminases elevation (ALT, AST >1000 IU/L)
- Signs of hepatic dysfunction

**Paracetamol Overdose (Fulminant Hepatic Failure - 72-96 hours):**

- Hepatic encephalopathy (confusion, lethargy, coma)
- Coagulopathy (INR >1.5)
- Severe hypoglycemia
- Acute renal failure
- Metabolic acidosis
- Multiorgan failure
- Death possible if untreated

**Phenylephrine Overdose:**

- Severe hypertension (BP >200/120 mmHg)
- Severe headache
- Chest pain/angina
- Palpitations, tachycardia
- Anxiety, agitation
- Tremor

- Potential cardiovascular events (MI, stroke)
- Potential hypertensive emergency

**Chlorpheniramine Overdose:**

- Severe CNS depression
- Deep sedation/somnolence progressing to coma
- Anticholinergic effects:
  - Severe dry mouth
  - Fixed, dilated pupils (mydriasis)
  - Tachycardia
  - Hypertension
  - Hyperthermia (fever)
  - Muscle rigidity
  - Seizures (in severe cases)
  - Rhabdomyolysis (rare)
- Paradoxical CNS stimulation (agitation, hallucinations) in some cases

**Management of Overdose:****Immediate Actions:**

1. **Stop medication immediately**
2. **Contact Poison Control Center or Emergency Services**
3. **Establish airway, breathing, circulation (ABC) support as needed**
4. **Obtain baseline vital signs and continuous monitoring**

**Gastric Decontamination (if appropriate timing - within 4 hours):**

- **Activated Charcoal:** 50 g orally (for single ingestions <24 hours prior). May repeat after 4-6 hours in severe cases. Caution: ineffective if patient has vomited extensively or has ileus.
- **Gastric Lavage:** Rarely indicated; consider if multiple tablets ingested within 2 hours and high-risk features present (severe hepatotoxicity risk).
- **Ipecac-induced Emesis:** NOT recommended; risk of aspiration, seizures; contraindicated with anticholinergic overdose

**Specific Antidote Therapy:****N-Acetylcysteine (NAC) for Paracetamol Overdose:**

- **Indication:** If paracetamol serum level indicates hepatotoxic risk (use Rumack-Matthew nomogram) OR if ingestion >7.5 g (15 tablets) AND <24 hours since ingestion
- **Loading Dose:** 150 mg/kg IV over 15-60 minutes (e.g., 10.5 g for 70 kg patient)
- **Second Dose:** 50 mg/kg IV over 4-16 hours
- **Maintenance Dose:** 100 mg/kg IV over 16-24 hours
- **Alternatively:** Oral NAC 140 mg/kg initial dose, then 70 mg/kg every 4 hours for 17 additional doses
- **Efficacy:** NAC most effective if started within 8 hours of overdose; benefit may persist up to 24 hours

**Symptomatic and Supportive Treatment:**

- **Fluid Resuscitation:** IV fluids for hypotension, dehydration; monitor electrolytes and acid-base balance
- **Monitoring:** Continuous cardiac monitoring, pulse oximetry, blood pressure monitoring
- **Laboratory Investigation:** Baseline and serial measurements:
  - Serum paracetamol level (at least 4 hours post-ingestion)
  - Liver function tests (AST, ALT, bilirubin, albumin)
  - Prothrombin time/INR
  - Serum creatinine, electrolytes, blood glucose
  - Arterial/venous blood gas analysis
  - Full blood count
- **Seizure Management:** Diazepam or lorazepam IV for seizure prophylaxis/treatment
- **Temperature Control:** Cooling measures for hyperthermia

- **Cardiac Arrhythmia Management:** Standard ACLS protocols; avoid medications that increase sympathomimetic effects
- **Blood Pressure Management:**
  - For Phenylephrine-induced hypertension: Phentolamine 5-10 mg IV bolus or nitroprusside/hydralazine infusion
  - For Chlorpheniramine-induced hypotension: IV fluids; consider norepinephrine or dopamine infusion
- **Hemodialysis:** Marginally beneficial for paracetamol; consider in severe cases with renal failure; phenylephrine and chlorpheniramine not efficiently dialyzed

#### Continued Monitoring and Follow-Up:

- Admit to Intensive Care Unit if any signs of hepatotoxicity, severe cardiovascular effects, or altered consciousness
- Monitor liver function daily for at least 5-7 days post-overdose
- Psychiatric evaluation if intentional overdose suspected
- Hepatology and Toxicology consultation for severe cases

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

#### Pharmacotherapeutic Group:

Other analgesics and antipyretics in combination with decongestant and antihistaminic agents

(ATC Code: N02BE51 or similar combination classification)

#### Mechanism of Action:

ColdReief™ Forte Effervescent exerts its therapeutic effects through the synergistic action of three pharmacologically distinct active ingredients:

#### A) Paracetamol (Acetaminophen):

- **Primary Mechanism:** Inhibition of prostaglandin synthesis via cyclooxygenase (COX) inhibition, particularly COX-3 in the central nervous system
- **Secondary Mechanism:** Modulation of serotonergic and monoaminergic neurotransmission in the brain
- **Pharmacological Effects:**
  - Analgesic: Raises pain perception threshold in the thalamus and hypothalamus
  - Antipyretic: Central action on hypothalamic temperature regulation center; reduces fever by increasing heat dissipation through vasodilation and sweating
  - Non-inflammatory: Unlike NSAIDs, minimal effect on peripheral prostaglandin synthesis; no significant anti-inflammatory activity or antiplatelet effects
- **Onset of Action:** 15-20 minutes (oral tablet); 10-15 minutes (effervescent formulation due to enhanced absorption)
- **Peak Effect:** 30-60 minutes
- **Duration of Action:** 4-6 hours

#### B) Phenylephrine Hydrochloride:

- **Primary Mechanism:** Selective alpha-1 adrenergic agonist
- **Receptor Binding:** High affinity for alpha-1A and alpha-1B adrenergic receptors; minimal beta-adrenergic or alpha-2 activity
- **Pharmacological Effects:**
  - Nasal Decongestant: Causes vasoconstriction of blood vessels in nasal mucosa, reducing mucosal edema and congestion
  - Mechanism of congestion relief: Decreases nasal blood flow and mucosal swelling, improving nasal airway patency
  - Systemic Effects: May cause mild elevation in blood pressure via systemic vasoconstriction (less pronounced than oral phenylephrine compared to IV/IM routes)
  - No Direct Bronchodilation: Unlike epinephrine, minimal direct effect on bronchial smooth muscle
- **Onset of Action:** 15-30 minutes (oral)
- **Peak Effect:** 30-90 minutes
- **Duration of Action:** 3-4 hours

- **Cardiovascular Effects Profile:**
  - Increases systolic and diastolic blood pressure
  - May cause reflex bradycardia (less common with alpha-1 selective agents)
  - Minimal direct cardiac effects

#### C) Chlorpheniramine Maleate:

- **Primary Mechanism:** Competitive antagonism at histamine H-1 receptors
- **Secondary Mechanism:** Anticholinergic (antimuscarinic) effects; sedative properties via CNS H-1 receptor antagonism
- **Pharmacological Effects:**
  - Antihistaminic: Blocks histamine-mediated effects in allergic and allergic-like responses
  - Reduces histamine-induced symptoms:
    - \* Sneezing and nasal symptoms
    - \* Watery/itchy eyes
    - \* Allergic rhinitis symptoms
    - \* Urticaria (mild cases)
  - Anticholinergic Effects: Results in:
    - \* Drying of respiratory tract secretions (useful in cold symptoms)
    - \* Drying of nasal secretions
    - \* Slight sedation (CNS depressant effect)
  - Sedative Effect: First-generation antihistamine; significant CNS penetration causes drowsiness
  - Anti-inflammatory: Minimal direct effect; secondary benefit through histamine blockade
- **Onset of Action:** 20-30 minutes (oral)
- **Peak Effect:** 1-2 hours
- **Duration of Action:** 4-12 hours (prolonged due to tissue binding)

#### Clinical Efficacy:

Numerous clinical studies demonstrate the efficacy of this fixed-dose combination:

#### Key Clinical Trial Findings:

Clinical Trial Evidence (Reference data from published studies on this combination):

- **Efficacy Parameters:** In a randomized controlled trial (420 adults with common cold), the combination demonstrated:
  - Reduction of total symptom score (TSS) from mean baseline 9.016 to 0.495 by day 5 (94.5% improvement)
  - 84.3% of patients achieved complete symptom relief by day 5
  - Statistically significant symptom reduction observed by day 1 ( $p < 0.0001$ )
  - Particular effectiveness against:
    - \* Nasal congestion: 91% relief rate
    - \* Headache/body pain: 88% relief rate
    - \* Fever: 86% relief rate
    - \* Sneezing/watery eyes: 79% relief rate
- **Comparative Studies:** Superior efficacy compared to placebo and equivalent or superior to other cold medications; faster onset of action compared to standard (non-effervescent) tablets
- **Tolerability:** Adverse event rate 13-15% with mostly minor, transient symptoms
- **Time to Symptom Relief:** Median time to meaningful symptom improvement: 1.5-2 hours

#### Immunological Effects:

This product does NOT contain immune-modulating agents and does NOT promote immune clearance of cold viruses. Benefits are purely symptomatic. The product is not expected to:

- Shorten duration of viral illness
- Reduce viral transmission
- Enhance immune response to infection
- Modify disease course

**Note:** Patients should understand that the medication provides symptomatic relief only and does not treat the underlying viral infection.

## 5.2 Pharmacokinetic Properties

### Absorption:

#### Paracetamol:

- **Route of Administration:** Oral (GI absorption)
- **Rate of Absorption:** Rapidly and completely absorbed from the gastrointestinal tract
- **Absorption Site:** Primarily duodenum and jejunum
- **Time to Peak Plasma Concentration (T<sub>max</sub>):** 30-60 minutes (standard tablets); 10-20 minutes (effervescent tablets)
- **Peak Plasma Concentration (C<sub>max</sub>):** 10-20 µg/mL (following 500 mg dose)
- **Bioavailability:** Approximately 70-90% (first-pass metabolism accounts for losses)
- **Effect of Food:** Minimal food effect; absorption may be slightly delayed but not significantly reduced
- **Effect of Formulation:** Effervescent formulation increases gastric pH and enhances dissolution, resulting in faster absorption (up to 50% faster onset) compared to standard tablets

#### Phenylephrine:

- **Rate of Absorption:** Irregular and relatively slow from GI tract; bioavailability approximately 40-50% due to first-pass hepatic metabolism
- **Time to Peak Concentration (T<sub>max</sub>):** 45-90 minutes (oral)
- **Peak Plasma Concentration (C<sub>max</sub>):** 1-2 ng/mL (following 10 mg oral dose)
- **Absolute Bioavailability:** 38% (approximately)
- **First-Pass Metabolism:** Substantial hepatic metabolism limits systemic availability
- **Effect of Food:** May be delayed or reduced by food intake; significant effect possible
- **Distribution:** Rapid distribution from intravascular to extravascular compartments

#### Chlorpheniramine:

- **Rate of Absorption:** Relatively rapid from GI tract
- **Time to Peak Concentration (T<sub>max</sub>):** 2-6 hours (wide variability between individuals)
- **Peak Plasma Concentration (C<sub>max</sub>):** 2-4 ng/mL (following 2 mg dose)
- **Bioavailability:** Approximately 25-45% (significant first-pass metabolism)
- **Effect of Food:** Variable effect; may delay absorption
- **CNS Penetration:** Significant; high lipophilicity allows crossing blood-brain barrier, contributing to CNS effects (sedation)

### Distribution:

#### Paracetamol:

- **Volume of Distribution (V<sub>d</sub>):** 0.5-1.0 L/kg (approximately 35-70 L in 70 kg patient)
- **Distribution:** Widespread distribution throughout body water
- **Protein Binding:** <20% (minimal protein binding)
- **CNS Penetration:** Readily crosses blood-brain barrier (responsible for CNS analgesic and antipyretic effects)
- **CSF Concentration:** Equilibrates with plasma; reaches 80-90% of plasma concentrations
- **Tissue Distribution:** Distributes equally to most tissues; accumulation not observed
- **Placental Transfer:** Crosses placenta; fetal concentrations approach maternal levels
- **Breast Milk:** Detected in breast milk; estimated <2% of maternal dose

#### Phenylephrine:

- **Volume of Distribution (V<sub>d</sub>):** 1.5-2.5 L/kg
- **Distribution:** Distributes to tissues; concentrates in cardiovascular system and target tissues (nasal mucosa)
- **Protein Binding:** Minimal (metabolized rapidly)
- **CNS Penetration:** Limited (polar structure); minimal CNS effects
- **Target Site Concentration:** High concentrations in nasal vasculature (local decongestant effect)

#### Chlorpheniramine:

- **Volume of Distribution (V<sub>d</sub>):** 3-5 L/kg

- **Protein Binding:** 70-80% (significant plasma protein binding)
- **CNS Penetration:** Highly lipophilic; significant blood-brain barrier penetration; tissue distribution throughout CNS
- **Tissue Binding:** Extensive binding in tissues, particularly CNS; may contribute to prolonged effects

**Metabolism:****Paracetamol:****Primary Metabolic Pathway (Major - 60-90% of dose):**

- **Conjugation with Glucuronic Acid:** Hepatic UDP-glucuronosyltransferase (UGT) catalyzes formation of paracetamol glucuronide (major metabolite, ~60% of dose)
- **Conjugation with Sulfuric Acid:** Hepatic phenol sulfotransferase (PST) catalyzes formation of paracetamol sulfate (~30% of dose)
- **Minor Pathway (5-10% of dose):** Cytochrome P450 oxidation (CYP2E1, CYP1A2, CYP3A4) produces toxic intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI)

**NAPQI Detoxification (Critical for Safety):**

- Normally rapidly conjugated with hepatic glutathione to form mercapturic acid conjugate (detoxified, excreted)
- At normal doses: All NAPQI is safely detoxified
- At overdose: Glutathione stores depleted → NAPQI accumulates → covalent binding to hepatocyte proteins → hepatocellular necrosis
- This explains why NAC therapy (provides cysteine for glutathione replenishment) is crucial in overdose

**Clinical Implications:**

- Genetic polymorphisms in UGT/PST affect metabolism rate (acetylation status)
- Enzyme induction (barbiturates, rifampin) increases CYP450 pathway and NAPQI formation → increased overdose risk
- Enzyme inhibition → slower metabolism, prolonged effects

**Phenylephrine:****Primary Pathway:** Monoamine oxidase (MAO) oxidative deamination in liver and intestinal wall

- MAO-A and MAO-B enzymes metabolize phenylephrine to inactive metabolites
- Rapid metabolism explains short half-life (~3-4 hours)
- Some oxidation by catechol-O-methyltransferase (COMT)

**Clinical Implications:**

- MAO inhibitor drugs → decreased phenylephrine metabolism → prolonged, enhanced effects → hypertensive crisis risk
- Genetic COMT variants may affect metabolism rate

**Chlorpheniramine:****Primary Pathway:** Hepatic oxidative metabolism

- N-demethylation: Major pathway producing desmethylchlorpheniramine (active metabolite with antihistaminic activity)
- Hydroxylation of aromatic rings
- CYP2D6 (variable expression) involved in metabolism → significant inter-individual variability
- Further conjugation (glucuronidation, sulfation) of metabolites

**Active Metabolites:**

- Desmethylchlorpheniramine is active antihistamine; may contribute to prolonged clinical effects
- Half-life of active metabolites longer than parent drug

**Clinical Implications:**

- CYP2D6 poor metabolizers: Higher plasma concentrations; prolonged effects; increased adverse effects
- CYP2D6 extensive metabolizers: Faster metabolism; potentially shorter duration of action
- Drug interactions affecting CYP2D6 may alter chlorpheniramine metabolism

**Elimination:****Paracetamol:**

- **Primary Route:** Renal excretion of metabolites (conjugates)
- **Elimination Pathway:**
  - Glucuronide conjugate (60%): Renal excretion

- Sulfate conjugate (30%): Renal excretion
- Mercapturic acid conjugate (5-10%): Renal excretion
- Small amount: Biliary excretion
- **Serum Half-Life:** 1-4 hours (depending on dose, hepatic function; doses at upper range have longer half-life due to saturation of conjugation pathways)
- **Plasma Clearance:** 10-20 mL/min/kg
- **Renal Clearance:** Approximately 4-6 mL/min (after conjugation)
- **Minimal Unchanged Drug:** <5% of dose excreted unchanged

**Phenylephrine:**

- **Primary Route:** Renal excretion of metabolites
- **Serum Half-Life:** 2.5-3.5 hours
- **Plasma Clearance:** 15-30 mL/min/kg (rapid due to intensive metabolism)
- **Minimal Unchanged Drug:** <5% excreted unchanged
- **Metabolite Excretion:** Inactive metabolites via urine

**Chlorpheniramine:**

- **Primary Route:** Renal excretion of metabolites
- **Serum Half-Life:** 12-43 hours (highly variable, average ~20-24 hours)
- **Elimination Rate:** Slower than paracetamol and phenylephrine; prolonged tissue retention contributes to long duration
- **Plasma Clearance:** 7-11 mL/min/kg
- **Minimal Unchanged Drug:** Minimal unchanged drug excretion; almost all excreted as metabolites
- **Accumulation Risk:** With frequent dosing (>4 hours intervals), accumulation possible due to long half-life; concerns if used continuously beyond 7 days

**Special Populations:****Hepatic Impairment:**

- **Paracetamol:** Significantly affected; metabolic clearance reduced; half-life prolonged; risk of accumulation; contraindicated in severe hepatic disease
- **Phenylephrine:** Moderately affected; hepatic clearance reduced; systemic exposure increased
- **Chlorpheniramine:** Significantly affected; first-pass metabolism reduced; plasma concentrations elevated; prolonged effects

**Renal Impairment:**

- **Paracetamol:** Moderate effect; conjugated metabolites accumulate; renal dose adjustment recommended in moderate to severe impairment
- **Phenylephrine:** Metabolites accumulate; minimal clinical significance (short-acting)
- **Chlorpheniramine:** Significant effect; metabolites accumulate; half-life prolonged from 20 hours to 40+ hours in severe renal impairment; dose reduction essential

**Elderly Patients:**

- **Paracetamol:** Clearance reduced; half-life increased (up to 4 hours); increased toxicity risk
- **Phenylephrine:** Systemic exposure increased; greater cardiovascular sensitivity
- **Chlorpheniramine:** Clearance reduced; prolonged effects; increased CNS sensitivity (enhanced sedation); increased anticholinergic effects

**Pregnancy:**

- **Paracetamol:** Clearance may be increased (up to 50%) due to hormonal effects on conjugation; no dose adjustment needed
- **Phenylephrine:** Limited data; no significant alterations expected
- **Chlorpheniramine:** Metabolism affected variably; no specific dosage recommendations established

**5.3 Preclinical Safety Data****General Toxicology:****Paracetamol:**

- **Acute Toxicity:**
  - LD50 (mouse, oral): 320 mg/kg
  - LD50 (rat, oral): 1,944 mg/kg
  - LD50 (rabbit, IV): 300 mg/kg
  - Acute toxicity primarily hepatotoxic (dose-dependent); not carcinogenic, mutagenic, or severely toxic at therapeutic doses
- **Repeat Dose Toxicity:** Hepatotoxicity observed at high doses; no specific organ toxicity at therapeutic doses
- **Known Clinical Safety:** Extensive human use history (>70 years); safety profile well-established clinically
- **Teratogenic/Reproductive Toxicity:** No evidence in animal studies; human data support safety in pregnancy
- **Carcinogenicity/Genotoxicity:** No evidence in animal studies; long human use history without carcinogenic concerns

#### Phenylephrine:

- **Acute Toxicity:**
  - LD50 (rat, IV): 20 mg/kg
  - LD50 (rat, oral): >5000 mg/kg (very high; reflects poor oral absorption)
  - Acute toxicity mainly cardiovascular (hypertensive effects)
- **Repeat Dose Toxicity:** At high doses, systemic hypertension and cardiac effects observed; no specific organ damage at therapeutic doses
- **Reproductive/Teratogenic:** Limited animal data; no teratogenic effects observed in available studies; some concern regarding placental vasoconstriction (not definitively demonstrated as teratogenic)
- **Carcinogenicity/Genotoxicity:** No evidence in available studies; no carcinogenic signals

#### Chlorpheniramine:

- **Acute Toxicity:**
  - LD50 (mouse, oral): 99-165 mg/kg
  - LD50 (rat, oral): 300-400 mg/kg
  - LD50 (rat, IV): 44 mg/kg
  - Acute toxicity primarily CNS (sedation, convulsions at high doses) and anticholinergic effects
- **Repeat Dose Toxicity:** No specific organ toxicity identified at therapeutic doses; CNS sensitization observed in some animal models
- **Reproductive/Teratogenic:** Some animal studies suggest possible developmental effects (not definitively teratogenic); no human malformations definitively attributed to first-generation antihistamines
- **Carcinogenicity/Genotoxicity:** No evidence; no carcinogenic signals in available studies

#### In Vitro Safety Data:

- **Mutagenicity (Ames Test):** Negative for all three active ingredients
- **Chromosomal Aberration:** Negative in Chinese hamster ovary cells
- **Micronucleus Test:** Negative (paracetamol, phenylephrine, chlorpheniramine)
- **Enzyme Induction:** Paracetamol not a significant inducer of CYP enzymes at therapeutic concentrations
- **Receptor Binding:** Phenylephrine shows selective alpha-1 receptor binding (as expected); chlorpheniramine shows H1-receptor antagonism (as expected)

#### Excipient Safety:

All excipients listed in Section 6.1 are well-established pharmaceutical excipients with documented safety profiles. Sodium content is the primary excipient safety consideration:

- Each tablet contains ~320 mg sodium; patients on sodium-restricted diets should consider this
- Aspartame content: Contains phenylalanine (warning for phenylketonuria patients)
- All other excipients at concentrations considered safe for pharmaceutical use

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Excipient	Function	Quantity per Tablet (mg)	Specification
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Sodium Bicarbonate	Base for effervescence	480	BP/USP
Tartaric Acid (Anhydrous)	Acid for effervescence	320	FCC/BP
Citric Acid (Anhydrous)	Acid for effervescence	250	FCC/BP
Sodium Carbonate	Base for effervescence	180	BP/USP
Microcrystalline Cellulose	Binder, diluent	200	USP
Croscarmellose Sodium	Disintegrant	80	USP
Magnesium Stearate	Lubricant	45	BP/USP
Stearic Acid	Lubricant	45	BP/USP
Aspartame	Sweetener	40	FCC/USP
Sodium Saccharin	Sweetener	15	BP/USP
Anhydrous Sodium Sulfate	Drying agent	30	BP/USP
Flavoring Agent (Lemon Oil/Extract)	Flavoring	25	FCC
Colorant (Sunset Yellow FCF/FD&C Yellow No. 6)	Coloring	5	FCC/E110
Povidone (K30)	Binder	50	BP/USP
Silicon Dioxide (Colloidal)	Anti-caking agent	20	USP
Talc (Purified)	Anti-adherent	15	BP/USP

**Note:** Excipients are used to achieve specific pharmaceutical functions in the effervescent tablet formulation. Batch-to-batch variability is minimized through strict specification controls. All excipients meet or exceed requirements of appropriate pharmacopeias (BP, USP, FCC, or equivalent).

## 6.2 Incompatibilities

### Physical Incompatibilities:

- ColdReief™ Forte Effervescent tablets should NOT be dissolved or mixed with other medicines in the same water before consumption
- Do not crush, chew, or dissolve tablets in acidic liquids (vinegar, citrus juices, cola)
- Dissolution in hot water (>50°C) may damage formulation; only room-temperature water recommended
- Do not mix with antacids in the same solution

### Chemical Incompatibilities:

#### Paracetamol:

- Incompatible with strong oxidizing agents (potassium permanganate, hydrogen peroxide, chlorine)
- Incompatible with phenolic compounds
- Sensitive to heat and humidity; stable in acidic to neutral conditions

#### Phenylephrine:

- Incompatible with alkaline solutions (pH >8)
- Oxidation-sensitive; incompatible with oxidizing agents
- May interact with iron salts (oxidation)
- Incompatible with strong reducing agents

#### Chlorpheniramine:

- Sensitive to light and oxidation
- Incompatible with strong oxidizing agents
- Incompatible with tannins
- Stable in acidic conditions; unstable in alkaline solutions

### Excipient Interactions:

- The combination of sodium bicarbonate, tartaric acid, citric acid, and sodium carbonate is specifically balanced for stable effervescence
- Moisture content must be strictly controlled (RH <30%) to prevent premature CO<sub>2</sub> release

- Interaction with metals: May form complexes with iron or heavy metals (storage containers must be aluminum-free or suitably coated)

### 6.3 Shelf Life

**Unopened Container:** 36 months from date of manufacture when stored under specified conditions (Section 6.4)

**After Opening:** Use entire contents within 14 days; leftover tablets should not be saved for future use

#### Excipient Degradation Timeline:

- Aspartame: Stable for full shelf-life under proper storage
- Colorants: Potential slight fading over time with light exposure (not affecting safety)
- Sodium bicarbonate/Sodium carbonate: Gradually react with atmospheric moisture and CO<sub>2</sub> (packaging integrity critical)

#### Stability Indicators (Signs of Degradation):

- Tablets appear crumbly or powdery (loss of structural integrity)
- Cloudiness or discoloration of solution when dissolved
- Weak or absent effervescence
- Unpleasant odor
- Any signs of mold or contamination

If any of above signs are observed, discard the product immediately.

### 6.4 Special Precautions for Storage

#### Storage Conditions:

- **Temperature:** Store at 15-25°C (59-77°F); do NOT store at temperatures exceeding 30°C
- **Humidity:** Store in a dry place; keep relative humidity below 30% (RH <30%)
- **Light Protection:** Protect from light; store in opaque container or in original packaging
- **Container:** Keep in original blister pack or foil-lined aluminum container; do not transfer to plastic bottles or paper containers
- **Moisture Protection:** Keep container tightly closed; do not open until time of use
- **Segregation:** Store away from oxidizing agents, strong acids, strong bases, and reducing agents
- **Temperature Extremes:** Do NOT freeze; do NOT refrigerate (condensation risk when returning to room temperature)
- **Ventilation:** Store in well-ventilated area; avoid closed, humid spaces

#### Storage Location Guidelines:

- Home: Bathroom medicine cabinet (if humidity controlled) or bedroom nightstand (preferred)
- Pharmacy/Hospital: Room-temperature storage in climate-controlled environment with RH <30%
- NOT recommended: Kitchen (moisture), bathroom without ventilation (humidity), direct sunlight, near heating sources

#### Transportation:

- Protect from temperature extremes during transport
- Avoid prolonged exposure to heat (>25°C)
- Use sealed containers; prevent exposure to high humidity environments
- Avoid transport in vehicles or locations subject to temperature fluctuations

### 6.5 Nature and Contents of Container

#### Primary Packaging:

- **Container Type:** Blister pack (PVC/PVDC (Aluminum backing) OR PVC/PE/PVDC laminate with aluminum foil backing)
- **Alternative Packaging:** Aluminum-Aluminum blister (most protective for moisture-sensitive effervescent tablets)
- **Tablet Position:** Each tablet individually wrapped in sealed cell
- **Container Closure:** Aluminum foil heat-sealed to blister film; ensures moisture protection and product integrity
- **Desiccant:** Silica gel desiccant packet included in outer carton (see Secondary Packaging)

#### Secondary Packaging (Carton):

- **Material:** Cardboard with moisture-resistant coating
- **Dimensions:** Standard pharmaceutical carton (typically 10 cm × 6 cm × 2.5 cm)
- **Contents:**
  - 1 blister pack containing 10 effervescent tablets (most common pack size)

- Product package insert (printed or inserted)
- Silica gel desiccant sachet (1-2 grams)
- Manufacturer information and expiry date label

**Disposal Instructions:****Patient Disposal at Home:**

- **Unused/Expired Tablets:**
  - Preferred method: Return to pharmacy for safe disposal program (many pharmacies participate in medication take-back programs)
  - If no pharmacy program available: Wrap tablets in paper, place in sealed plastic bag, mixed with undesirable substance (coffee grounds, flour, kitty litter) to make medication unpalatable, then place in household garbage
  - Alternative: Follow local pharmaceutical disposal guidelines if available
  - Do NOT flush tablets down toilet unless specifically labeled as flushable
  - Do NOT pour dissolved solution down drain; flush with plenty of water
- **Expired Blister Packs:** May be torn open and tablets disposed of as above; blister pack material may be recycled as cardboard/aluminum (check local recycling guidelines)

**Healthcare Facility Disposal:**

- All unused, expired, or returned-by-patient tablets must be accumulated in designated pharmaceutical waste container
- Container must be labeled "Pharmaceutical Waste - Do Not Incinerate with General Waste"
- Arrange disposal with certified hazardous/pharmaceutical waste contractor
- Document destruction with certificate of destruction maintained in facility records
- DO NOT dispose down hospital drain systems
- DO NOT mix with radioactive or cytotoxic waste
- Disposal must comply with:
  - Environmental Protection Agency (EPA) regulations
  - Local/state pharmacy board regulations
  - Institutional policies and procedures

**Environmental Considerations:**

- Paracetamol, phenylephrine, and chlorpheniramine are not considered highly persistent in environment
- Excipients (sodium salts, citric acid, tartaric acid) are biodegradable
- Avoid environmental contamination through proper waste disposal

**7. MARKETING AUTHORISATION HOLDER**

**Company Name:** Pharmacare Pharmaceuticals Ltd.

**Registered Address:**

Innovation House, Plot No. 567  
Pharma Park, Karkhana Road  
Amsterdam, 1025 AB  
Netherlands

**Company Background:**

Pharmacare Pharmaceuticals Ltd. is a leading European pharmaceutical company specializing in over-the-counter (OTC) and prescription medicines. Founded in 2005, the company operates manufacturing facilities across European Union (Netherlands, Germany) and India. The company is ISO 13485, ISO 9001 certified, and maintains GMP (Good Manufacturing Practice) compliance across all facilities. ColdReief™ Forte Effervescent is one of Pharmacare's flagship OTC cold and flu symptomatic relief products, available in 35+ countries across Europe, Asia, and Africa.

**8. MARKETING AUTHORISATION NUMBER(S)**

Pharmacare Pharmaceuticals Ltd.: EU/1/2022/045/001 (European Union)

Pharmacare Pharmaceuticals Ltd.: NL-10075-2022 (Netherlands)

#### 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

**Initial/First Authorisation:** 15 March 2022

**Regulatory Route:** Centralized Procedure via European Medicines Agency (EMA) for European Union authorisation; individual national procedures for specific member states and other countries

**Authorisation Status:** Active

**Expiry Date of Current Authorisation:** 14 March 2027 (5-year authorization period)

#### 10. DATE OF REVISION OF THE TEXT

**Current Revision Date:** 15 December 2024