SUMMARY OF MEDICINAL PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

ComfortCold Plus™ Sachets

1.1 Strength and Composition

ComfortCold Plus™ 325 mg / 10 mg / 5 mg / 2 mg Sachets

Pharmaceutical Active Ingredients per Sachet:

- Acetaminophen (Paracetamol) - 325 mg (Analgesic/Antipyretic)
- Dextromethorphan Hydrobromide - 10 mg (Cough Suppressant)
- Phenylephrine Hydrochloride - 5 mg (Nasal Decongestant)
- Chlorpheniramine Maleate - 2 mg (Antihistamine)

1.2 Pharmaceutical Form

Oral Powder for Suspension - Instant Dissolving Sachets

Presentation: Individual single-dose sachets containing effervescent powder for oral administration after dissolution in hot water.

Sachet Volume: 5.5 grams (gross weight per sachet)
Appearance: White to off-white granular powder with pleasant lemon-menthol flavor profile

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Active Pharmaceutical Ingredients (API):

1. **Acetaminophen (Paracetamol)** - INN: Paracetamol
    - Chemical Name: N-(4-Hydroxyphenyl)acetamide
    - CAS Number: 103-90-2
    - Molecular Formula: $C_8H_9NO_2$
    - Molecular Weight: 151.16 g/mol
    - Quality: European Pharmacopoeia (Ph.Eur.) Standard / USP Standard
2. **Dextromethorphan Hydrobromide (DXM HBr)** - INN: Dextromethorphan
    - Chemical Name: (1R,5S,6R)-1,5-Dimethyl-6-(2-phenylpropan-2-yl)cyclohex-3-enol Hydrobromide
    - CAS Number: 125-69-9
    - Molecular Formula: $C_{18}H_{25}NO \cdot HBr$
    - Molecular Weight: 352.31 g/mol

- Quality: USP / Ph.Eur. Standard

3. **Phenylephrine Hydrochloride (PE HCl)** - INN: Phenylephrine
    - Chemical Name: 1-(4-Hydroxyphenyl)-2-(methylamino)ethanol Hydrochloride
    - CAS Number: 59-42-7
    - Molecular Formula: $C_9H_{13}NO_2 \cdot HCl$
    - Molecular Weight: 203.67 g/mol
    - Quality: USP / Ph.Eur. Standard
4. **Chlorpheniramine Maleate** - INN: Chlorpheniramine
    - Chemical Name: 3-(2-Chloro-10H-phenothiazin-10-yl)-N,N-dimethylpropan-1-amine Maleate
    - CAS Number: 113-92-8
    - Molecular Formula: $C_{16}H_{19}ClN_2S \cdot C_4H_4O_4$
    - Molecular Weight: 390.87 g/mol
    - Quality: USP / Ph.Eur. Standard

2.2 Quantitative Declaration

Per Single Sachet (5.5 g):

Active Ingredient	Quantity	Quality Standard	Function
Acetaminophen	325 mg	Ph.Eur./USP	Analgesic/Antipyretic
Dextromethorphan HBr	10 mg	USP/Ph.Eur.	Antitussive (Cough Suppressant)
Phenylephrine HCl	5 mg	USP/Ph.Eur.	Nasal Decongestant
Chlorpheniramine Maleate	2 mg	USP/Ph.Eur.	Antihistamine (Sedating)

2.3 Excipients (Inactive Ingredients)

List of Excipients with Known Effects:

Excipient Name	**Quantity/Sachet**	**Pharmacopeial Standard**	
Citric Acid Anhydrous	800 mg	Ph.Eur./USP	
Sodium Bicarbonate	650 mg	Ph.Eur./USP	
Sodium Carbonate Anhydrous	450 mg	Ph.Eur./USP	
Lactose Monohydrate	800 mg	Ph.Eur./USP	
Microcrystalline Cellulose (Avicel PH101)	500 mg	Ph.Eur./USP	
Croscarmellose Sodium	120 mg	Ph.Eur./USP	
Magnesium Stearate	45 mg	Ph.Eur./USP	
Silicon Dioxide (Colloidal)	80 mg	Ph.Eur./USP	
Aspartame	30 mg	Ph.Eur./USP	
Lemon Flavor (Natural	Synthetic)	60 mg	FCC/Ph.Eur.
Menthol (L-Menthol)	25 mg	Ph.Eur./USP	
Sucrose (Pulverized)	300 mg	Ph.Eur./USP	
Acacia Gum (Gum Arabic)	45 mg	Ph.Eur./USP	
Ascorbic Acid (Vitamin C)	35 mg	Ph.Eur./USP	
Talc (Magnesium Silicate)	50 mg	Ph.Eur./USP	

Sunset Yellow FCF (E110)	2 mg	Ph.Eur./USP	
Saccharin Sodium	15 mg	Ph.Eur./USP	

Table 1: Complete Excipient Composition

Known Effects of Excipients:

- **Lactose Monohydrate**: May cause gastrointestinal discomfort in patients with lactose intolerance
- **Aspartame**: Contains phenylalanine; contraindicated in phenylketonuria (PKU)
- **Sodium Content**: Total sodium per sachet = 245 mg (approximately 10.6% of WHO recommended maximum daily intake)
- **Sucrose**: Contains fermentable carbohydrates; patients with hereditary fructose intolerance should avoid

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3. PHARMACEUTICAL FORM

Oral Powder for Suspension - Effervescent Sachet

Physical Description:

- **Form**: Granular effervescent powder
- **Color**: White to off-white with slight yellow tint (from sunset yellow colorant)
- **Odor**: Lemon-menthol aromatic
- **Taste**: Pleasant lemon-menthol with slight sweetness
- **Solubility**: Rapidly dissolves in hot water (60-80°C) within 2-3 minutes
- **Stability**: Maintains physical integrity and appearance for 36 months at 25°C/60% RH

Method of Reconstitution:

Dissolve entire contents of one sachet in 200 mL of hot water, stir for 30 seconds, and allow to cool to optimal drinking temperature (approximately 45-50°C).

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4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ComfortCold Plus™ is indicated for the temporary relief of the following symptoms associated with the common cold, influenza, allergic rhinitis, and upper respiratory tract conditions:

- Cough (nonproductive)
- Nasal congestion and sinus pressure
- Sneezing and rhinorrhea (runny nose)
- Headache and body aches
- Sore throat pain
- Elevated body temperature (fever)
- Itchy and watery eyes associated with allergic rhinitis

- General malaise and fatigue related to respiratory viral infections

4.2 Posology and Method of Administration

Dosage Recommendations:

Adults and Adolescents (16 years and older):

- **Standard Dose**: One sachet every 4-6 hours as required for symptomatic relief
- **Maximum Daily Dose**: Not more than 4 sachets in a 24-hour period
- **Maximum Duration**: Not to exceed 5 consecutive days without medical consultation
- **Route**: Oral administration following dissolution in hot water
- **Method**: Stir sachet contents in approximately 200 mL of hot water until completely dissolved; may be sweetened to taste if desired

Elderly Patients (≥65 years):

- Standard adult dosage is generally appropriate
- However, dose reduction may be considered in:
    - Patients with renal impairment (eGFR <60 mL/min/1.73m²)
    - Patients with hepatic impairment (Child-Pugh Class B or C)
    - Frail or immobile elderly subjects
- Medical consultation recommended before use

Pediatric Use:

- **Children under 16 years**: DO NOT USE. Consult physician for age-appropriate formulations.
- The combination and dosage strength of this product is not suitable for children below 16 years of age.

Method of Administration:

Step-by-Step Instructions:

1. Tear open sachet carefully along the perforated edge
2. Pour powder into 200 mL cup of hot water (60-80°C)
3. Stir vigorously for 30 seconds until completely dissolved
4. Allow to cool to comfortable drinking temperature (45-50°C)
5. Drink immediately; do not store prepared solution
6. Rinse cup with water and drink if residue remains
7. Do not exceed 4 sachets per 24-hour period
8. Space doses at least 4 hours apart

Important Administration Notes:

- Always dissolve in water; never consume powder directly
- Do not exceed recommended dosing frequency
- Do not combine with other acetaminophen-containing products

- Take with or without food; if gastric upset occurs, take with light meal
- Do not use heating devices (microwave) for water preparation; use standard kettle

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4.3 Contraindications

ComfortCold Plus™ is contraindicated in patients with:

- **Hypersensitivity** to acetaminophen, dextromethorphan hydrobromide, phenylephrine hydrochloride, chlorpheniramine maleate, or any excipients listed in section 6.1
- **Phenylketonuria (PKU)** due to aspartame content containing phenylalanine
- **Severe Cardiac Conditions**: Severe coronary heart disease, uncontrolled hypertension (systolic BP >180 mmHg), or significant cardiovascular disorders
- **Pheochromocytoma**: Due to sympathomimetic activity of phenylephrine
- **Angle-Closure Glaucoma**: Chlorpheniramine may precipitate acute attack; phenylephrine may elevate intraocular pressure
- **Diabetes Mellitus**: Relative contraindication; phenylephrine may affect glycemic control
- **Concurrent MAOI Therapy**: Monoamine oxidase inhibitors used for depression or Parkinson's disease; minimum 14-day washout required after MAOI discontinuation before use
- **Severe Hepatic Impairment**: Child-Pugh Class C cirrhosis; acetaminophen contraindicated
- **Severe Renal Impairment**: eGFR <15 mL/min/1.73m²
- **Lactose Intolerance**: Complete lactose intolerance or galactose malabsorption syndrome
- **Chronic Respiratory Conditions**: Severe asthma, COPD with respiratory depression, or emphysema
- **Sleep Apnea**: Dextromethorphan may depress respiration
- **Urinary Retention**: Benign prostatic hyperplasia with urinary hesitancy or retention
- **Concurrent Warfarin Therapy**: Increased bleeding risk with acetaminophen; medical consultation required

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4.4 Special Warnings and Precautions for Use

Special Precautions:

Hepatotoxicity Risk (Acetaminophen):

- Maximum daily dose of acetaminophen should not exceed 4 g/day in adults, which equals 4 sachets of ComfortCold Plus™
- Caution in patients with:
    - Chronic alcohol consumption (≥3 drinks daily)
    - Existing liver disease (hepatitis B, hepatitis C, cirrhosis)
    - Chronic malnutrition or fasting states
    - Severe dehydration
- Patients should be advised of signs of hepatotoxicity: persistent nausea, upper right abdominal pain, jaundice, dark urine

Cardiovascular Precautions (Phenylephrine):

- Use with caution in patients with:
  - Mild to moderate hypertension (SBP 140-180 mmHg)
  - Coronary artery disease without active symptoms
  - Cardiac arrhythmias or palpitations
  - Thyroid disorders (hyperthyroidism)
  - Raynaud's phenomenon - may exacerbate vasospasm
- Phenylephrine may cause transient elevation in blood pressure; monitoring recommended in susceptible patients
- May cause reflex tachycardia in some individuals

CNS Precautions (Dextromethorphan & Chlorpheniramine):

- May cause drowsiness and impair mental/motor alertness
- Operating machinery or driving motor vehicles should be avoided until individual tolerance established
- Risk of sedation increased with:
  - Concurrent sedatives, tranquilizers, or CNS depressants
  - Alcohol consumption
  - Age >65 years
- Potential for abuse or overdose with dextromethorphan in susceptible populations

Respiratory Precautions:

- Dextromethorphan may depress respiratory drive in:
  - Patients with pre-existing respiratory depression
  - Chronic obstructive pulmonary disease (COPD) patients
  - Asthmatic patients - paradoxical bronchoconstriction possible
  - Sleep apnea syndrome

Renal Function:

- eGFR 30-59 mL/min/1.73m²: Standard dosing acceptable with monitoring
- eGFR 15-29 mL/min/1.73m²: Dose reduction recommended (maximum 1 sachet every 6-8 hours)
- eGFR <15 mL/min/1.73m²: Contraindicated; requires dialysis assessment

Hepatic Function:

- Child-Pugh Class A: Standard dosing acceptable
- Child-Pugh Class B: Consider dose reduction (maximum 1-2 sachets daily)
- Child-Pugh Class C: Contraindicated

Patient Counseling Points:

Patients should be informed:

1. Do not exceed 4 sachets per 24-hour period
2. Do not use for more than 5 days continuously without medical assessment
3. Avoid all other acetaminophen-containing products (prescription and OTC)
4. Do not drive or operate heavy machinery if drowsiness occurs
5. Avoid alcohol consumption while using this product
6. Report persistent cough lasting >1 week as may indicate serious underlying condition
7. Seek immediate medical attention if experiencing severe allergic reactions, chest pain, breathing difficulty, or signs of overdose
8. Inform healthcare provider of all concurrent medications and medical conditions
9. Product contains aspartame; inform patients with PKU
10. Product contains sodium (245 mg per sachet); patients on sodium-restricted diet should consult physician

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4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Major Drug Interactions (Contraindicated):

Monoamine Oxidase Inhibitors (MAOIs):

- **Mechanism**: Phenylephrine may cause severe hypertensive crisis when combined with MAOIs
- **Examples**: Phenelzine, Tranylcypromine, Isocarboxazid, Moclobemide
- **Recommendation**: Contraindicated; wait minimum 14 days after MAOI discontinuation
- **Risk Level**: HIGH

Linezolid (Antibiotic):

- **Mechanism**: MAOI-like activity; combined sympathomimetic effects
- **Recommendation**: Avoid concurrent use; supervise carefully if unavoidable
- **Risk Level**: HIGH

Moderate Drug Interactions:

Warfarin and Other Anticoagulants:

- **Acetaminophen Effect**: May potentiate anticoagulant effect; increased bleeding risk
- **Clinical Significance**: Prolonged INR elevation possible
- **Recommendation**: Medical consultation required; INR monitoring recommended
- **Dosing Adjustment**: Consider dose reduction or alternative analgesic
- **Risk Level**: MODERATE

Tricyclic Antidepressants (TCAs):

- **Examples**: Amitriptyline, Nortriptyline, Imipramine
- **Mechanism**: Additive anticholinergic and sedative effects
- **Symptoms to Monitor**: Excessive sedation, urinary retention, constipation, dry mouth

- **Recommendation**: Use with caution; supervise dosing
- **Risk Level**: MODERATE

Selective Serotonin Reuptake Inhibitors (SSRIs):

- **Examples**: Sertraline, Fluoxetine, Paroxetine
- **Mechanism**: Potential serotonin syndrome with dextromethorphan
- **Symptoms**: Agitation, confusion, rapid heart rate, elevated temperature, muscle rigidity
- **Recommendation**: Monitor closely; consider alternative products
- **Risk Level**: MODERATE

Sedative/Hypnotic Agents:

- **Examples**: Benzodiazepines (diazepam, lorazepam), Zolpidem, Zopiclone
- **Mechanism**: Additive CNS depression via chlorpheniramine
- **Effect**: Enhanced drowsiness, impaired cognition, respiratory depression risk
- **Recommendation**: Avoid concurrent use if possible; warn against driving
- **Risk Level**: MODERATE

Alcohol:

- **Mechanism**: Additive CNS depression and hepatotoxicity risk
- **Clinical Significance**: Greatly increased drowsiness, impaired judgment, liver damage potential
- **Recommendation**: Strong advise against alcohol consumption during use
- **Risk Level**: MODERATE

Minor Drug Interactions:

Anticholinergic Medications:

- **Examples**: Antihistamines (H1-blockers), Atropine, Scopolamine, Antispasmodics
- **Mechanism**: Additive anticholinergic effects via chlorpheniramine
- **Symptoms**: Dry mouth, constipation, urinary retention, blurred vision
- **Recommendation**: Use with monitoring; reduce dose if necessary
- **Risk Level**: MINOR

Sympathomimetic Decongestants:

- **Examples**: Pseudoephedrine, Ephedrine, Phenylpropanolamine
- **Mechanism**: Additive sympathomimetic effects with phenylephrine
- **Symptoms**: Hypertension, tachycardia, tremor, anxiety
- **Recommendation**: Do not combine products; use one decongestant only
- **Risk Level**: MINOR

Proton Pump Inhibitors (PPIs):

- **Examples**: Omeprazole, Lansoprazole, Pantoprazole

- **Mechanism**: May alter absorption of dextromethorphan metabolites
- **Clinical Significance**: Minimal; may slightly increase DXM levels
- **Recommendation**: Standard monitoring sufficient
- **Risk Level**: MINOR

Antidiabetic Agents:

- **Examples**: Metformin, Glipizide, Insulin
- **Mechanism**: Phenylephrine may elevate blood glucose; counteract antidiabetic effect
- **Recommendation**: Monitor blood glucose; dose adjustment possible
- **Risk Level**: MINOR

Thyroid Hormone Replacement:

- **Example**: Levothyroxine
- **Mechanism**: Phenylephrine may enhance sensitivity to thyroid hormone
- **Recommendation**: Standard monitoring; notify endocrinologist of use
- **Risk Level**: MINOR

Effects on Laboratory Tests:

- **Urine Drug Screening**: Dextromethorphan may produce false-positive for phencyclidine (PCP) on some assays
- **Platelet Function**: Acetaminophen may affect bleeding time in some individuals
- **Liver Function Tests**: Chronically may cause mild elevation in hepatic enzymes
- **Blood Glucose**: Phenylephrine may cause transient hyperglycemia

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4.6 Fertility, Pregnancy, and Lactation

Pregnancy:

Category B (Based on Available Evidence):

Acetaminophen:

- Extensive clinical use in pregnancy without documented adverse fetal effects
- Animal studies show no reproductive toxicity
- Category: FDA Pregnancy Category B
- Recommendation: Acceptable in pregnancy, particularly for short-term use (≤5 days)
- Can be used for fever reduction and pain relief during all trimesters

Dextromethorphan:

- Limited human pregnancy data; animal studies negative for teratogenicity
- Category: FDA Pregnancy Category C
- Historical use without documented adverse outcomes

- Recommendation: Use only if clearly necessary; benefits must outweigh potential risks
- Generally avoided in first trimester if possible

Phenylephrine:

- Limited reproductive data; potential concern for vasoconstriction affecting placental blood flow
- Category: FDA Pregnancy Category C
- Animal studies show no clear fetal harm
- Recommendation: Use with caution; generally avoid in first trimester
- Risk of congenital anomalies not clearly established but theoretical concern

Chlorpheniramine:

- Sedating antihistamines (first-generation) used extensively in pregnancy
- Category: FDA Pregnancy Category B
- Extensive safety data supporting use in pregnancy
- Recommendation: Generally acceptable; preferred over non-sedating antihistamines in pregnancy
- May cause mild neonatal effects if used near delivery

Overall Pregnancy Recommendation:
ComfortCold Plus™ is generally acceptable for short-term symptom management in pregnancy (maximum 5 days), particularly for fever reduction and nasal congestion relief. However, use should be limited to situations where benefits clearly outweigh risks, and medical consultation is recommended before use in pregnancy.

Lactation:

Excretion in Breast Milk:

- **Acetaminophen**: Excreted in breast milk in small amounts (peak 1-2 hours post-dose); amount approximately 0.1-0.2% of maternal dose
- **Dextromethorphan**: Minimal excretion in breast milk; limited data available
- **Phenylephrine**: Minimal excretion in breast milk; primarily metabolized
- **Chlorpheniramine**: Excreted in breast milk in variable amounts; theoretical potential for sedation in nursing infant

Safety Assessment:

- Lactation Category: Generally Recognized as Safe (GRAS) for short-term use
- Risk to nursing infant is minimal with standard dosing
- No documented adverse effects in nursing infants with short-term use

Recommendation:
ComfortCold Plus™ may be used during lactation for short-term symptom relief (maximum 5 days). However, alternative single-ingredient products (acetaminophen or phenylephrine alone) may be preferred to minimize infant exposure. If drowsiness develops in nursing infant, discontinue use and consult healthcare provider.

Fertility:

No evidence of impairment of fertility with any component in ComfortCold Plus™ at recommended therapeutic doses. Animal studies show no adverse effects on reproductive function or male/female fertility parameters.

4.7 Effects on Ability to Drive and Operate Machinery

Caution Advised:

ComfortCold Plus™ may cause drowsiness, dizziness, or impaired visual acuity, particularly due to the sedating antihistamine component (chlorpheniramine 2 mg per sachet).

Risk Factors for Impairment:

- First-time users; tolerance develops over first 2-3 doses
- Elderly patients (>65 years)
- Concurrent alcohol consumption
- Concurrent sedative/hypnotic use
- Renal or hepatic impairment
- Doses at upper end of recommended range

Patient Instructions:

- Do not drive motor vehicles if drowsiness develops
- Do not operate heavy or precision machinery
- Avoid activities requiring alertness until individual response is established
- Inform patients that impairment may not be apparent to them
- Caution regarding interaction with alcohol (significantly increases impairment)

Medical Professional Guidance:
Healthcare providers should advise patients of potential drowsiness and impairment before dispensing, particularly for:

- Commercial drivers (bus, truck, taxi)
- Operating room personnel
- Heavy machinery operators
- Pilots or aviation personnel

4.8 Undesirable Effects (Adverse Reactions)

Adverse events reported with ComfortCold Plus™ and its components are listed below, tabulated by system organ class and frequency.

Frequency Definitions (ICH-GCP):

- **Very Common**: ≥1/10 (≥10%)
- **Common**: ≥1/100 and <1/10 (1-10%)
- **Uncommon**: ≥1/1,000 and <1/100 (0.1-1%)

- **Rare**: ≥1/10,000 and <1/1,000 (0.01-0.1%)
- **Very Rare**: <1/10,000 (<0.01%)
- **Not Known**: Cannot be estimated from available data

Adverse Reactions by System Organ Class:

Immune System Disorders:

- **Uncommon**: Allergic reactions (rash, urticaria, pruritus), angioedema
- **Rare**: Anaphylaxis, severe hypersensitivity reactions
- **Not Known**: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis (associated with acetaminophen)

Nervous System:

- **Common**: Drowsiness, sedation, dizziness, headache (sometimes exacerbation of presenting headache)
- **Uncommon**: Tremor, nervousness, excitability (particularly in children with chlorpheniramine)
- **Rare**: Confusion, hallucinations, convulsions (dextromethorphan overdose), peripheral neuropathy
- **Not Known**: Serotonin syndrome (with concurrent SSRIs)

Eye Disorders:

- **Common**: Blurred vision, accommodation disorders, dry eyes (anticholinergic effects)
- **Uncommon**: Photophobia, temporary vision changes
- **Rare**: Acute angle-closure glaucoma (contraindicated), mydriasis

Cardiac/Vascular:

- **Common**: Palpitations, tachycardia (phenylephrine-induced)
- **Uncommon**: Hypertension, flushing, chest tightness
- **Rare**: Severe hypertension, arrhythmias, myocardial infarction (in predisposed)
- **Very Rare**: Cardiovascular collapse (with overdose or MAOI interaction)

Respiratory System:

- **Common**: None expected with recommended dosing
- **Uncommon**: Dyspnea, chest tightness
- **Rare**: Respiratory depression (dextromethorphan), bronchospasm
- **Not Known**: Severe respiratory depression (with MAOI or high-dose overdose)

Gastrointestinal:

- **Common**: Nausea, constipation (antihistamine), dry mouth
- **Uncommon**: Vomiting, abdominal pain, diarrhea, dyspepsia
- **Rare**: Gastrointestinal hemorrhage (with warfarin interaction)
- **Not Known**: Hepatotoxicity (acetaminophen overdose), acute liver failure

Hepatobiliary:

- **Rare**: Elevated liver enzymes (AST/ALT), jaundice
- **Very Rare**: Acute liver failure, hepatic necrosis (acetaminophen overdose)
- **Not Known**: Fulminant hepatitis (acetaminophen >4 g/day chronically or overdose)

Renal and Urinary:

- **Uncommon**: Dysuria, urinary hesitancy, urinary retention (anticholinergic effects)
- **Rare**: Acute kidney injury (severe dehydration), hematuria
- **Not Known**: Acute tubulointerstitial nephritis (acetaminophen)

Endocrine:

- **Uncommon**: Hyperglycemia (phenylephrine)
- **Rare**: Inappropriate antidiuretic hormone secretion (SIADH)

Musculoskeletal:

- **Rare**: Muscle rigidity (dextromethorphan at high doses), myalgia

General/Administrative:

- **Common**: Fatigue, asthenia, malaise (usually from underlying viral infection)
- **Uncommon**: Fever (rebound), chills
- **Rare**: Thermoregulation disturbance

Overdose Adverse Reactions:

Signs and Symptoms of Overdose:

- **Mild to Moderate**: Nausea, vomiting, abdominal pain, drowsiness, dizziness, tachycardia, tremor
- **Severe**: Hepatotoxicity (elevated enzymes, jaundice, hepatic necrosis), severe CNS depression, respiratory depression, seizures, arrhythmias, coma, organ failure

Critical Sign - Severe Acetaminophen Overdose:

- Phase 1 (0-24 hours): Nausea, vomiting, abdominal pain, diaphoresis, pallor
- Phase 2 (24-48 hours): Apparent clinical improvement; elevated liver enzymes (AST, ALT); right upper quadrant pain
- Phase 3 (48-96 hours): Hepatotoxicity manifests; elevated bilirubin, INR; potential hepatic failure
- Phase 4 (96+ hours): Recovery or fulminant hepatic failure; encephalopathy, coagulopathy, coma, death

Reporting of Suspected Adverse Reactions:

Healthcare professionals are urged to report any suspected adverse reactions to regulatory authorities:

- **USA (FDA)**: MedWatch program (1-800-FDA-1088) or www.fda.gov/medwatch
- **EU**: EudraVigilance system through national pharmacovigilance centers
- **Canada**: Health Canada Adverse Reaction Database (1-866-234-2345)

4.9 Overdose

Symptoms and Signs:

Mild Overdose (Up to 6 sachets / 1.95 g acetaminophen):

- Nausea and vomiting
- Abdominal pain (right upper quadrant)
- Sweating
- Mild tachycardia
- Drowsiness, sedation
- Dizziness, tremor

Moderate Overdose (6-10 sachets / 1.95-3.25 g acetaminophen):

- Severe nausea and vomiting
- Significant abdominal pain
- Hepatic enzyme elevation (AST, ALT)
- Marked drowsiness and CNS depression
- Potential respiratory depression
- Hypertension or hypotension
- Tachycardia or arrhythmias
- Confusion, agitation

Severe Overdose (>10 sachets / >3.25 g acetaminophen):

- **Acute Phase (0-24 hours)**: Severe nausea/vomiting, abdominal pain, diaphoresis, potential altered consciousness
- **Hepatotoxic Phase (24-72 hours)**: Jaundice, hepatomegaly, elevated liver enzymes (AST/ALT >1000 IU/L), coagulopathy (elevated INR)
- **Fulminant Hepatic Failure Phase (>72 hours)**: Encephalopathy, severe coagulopathy, hypoglycemia, renal failure, cerebral edema, potential death

Management and Treatment:

Immediate Actions (First 4 Hours):

1. **Gastrointestinal Decontamination**:
    - Activated charcoal: 25-100 g orally or via nasogastric tube (most effective if given within 2 hours)
    - Do NOT induce vomiting
    - Consider gastric lavage if presentation within 1 hour of ingestion
2. **Antidote - N-Acetylcysteine (NAC)**:
    - **Dosing**: Loading dose: 140 mg/kg orally, then 70 mg/kg every 4 hours for 17 doses

- **Alternative (IV NAC)**: Loading dose: 150 mg/kg over 60 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours
- **Timing**: Most effective if initiated within 8-10 hours of overdose; effective up to 24 hours
- **Mechanism**: Replenishes depleted hepatic glutathione stores; enhances acetaminophen metabolism

3. **Supportive Care**:
    - Maintain airway, breathing, and circulation
    - Fluid resuscitation with IV normal saline
    - Correction of hypoglycemia with IV dextrose
    - Antiemetics for nausea/vomiting (ondansetron, metoclopramide)
    - Monitoring of vital signs and cardiac rhythm
    - Temperature management if hyperthermic

Laboratory Monitoring:

- **Baseline (Immediate)**: Serum acetaminophen level (critical if <4 hours post-ingestion; use to assess risk via Rumack-Matthew nomogram), AST, ALT, bilirubin, INR, creatinine, blood glucose, CBC, blood gas analysis
- **Serial Monitoring (Every 12-24 hours)**: AST, ALT, bilirubin, INR, creatinine, blood glucose, arterial or venous blood gas
- **Acetaminophen Serum Level Interpretation**:
    - <10 mcg/mL at 4 hours post-ingestion: Minimal risk
    - 200 mcg/mL at 4 hours: High risk; NAC indicated
    - 100 mcg/mL at 8 hours: NAC strongly recommended
    - 50 mcg/mL at 12 hours: NAC indicated
    - 25 mcg/mL at 16 hours: NAC indicated

Specific Toxin Management:

For Dextromethorphan Toxicity:

- Risk of overdose particularly with >30 mg (>3 sachets)
- Management: Supportive care, monitoring of respiratory function
- Potential for "robo-tripping" (recreational abuse) with very high doses
- CNS effects managed with benzodiazepines if seizures occur

For Phenylephrine Toxicity:

- Risk of severe hypertension, arrhythmias
- Management: Alpha-blockers (phentolamine) for hypertensive crisis (initial dose 5 mg IV for symptomatic hypertension >180 mmHg SBP)
- Beta-blockers contraindicated as monotherapy (risk of unopposed alpha-adrenergic effect)
- Vasodilators (nitroprusside, nitroglycerin) as adjuncts

For Chlorpheniramine Toxicity:

- Risk of anticholinergic toxidrome or paradoxical excitation
- Management: Benzodiazepines for agitation, seizure prophylaxis
- Physostigmine (cholinesterase inhibitor) controversial; consider only for severe anticholinergic symptoms
- Supportive care and monitoring

Follow-up Care:

- Liver function assessment at 24, 48, and 72 hours post-overdose
- Hepatology consultation if INR >1.5 or clinical evidence of liver dysfunction
- ICU admission if signs of fulminant hepatic failure develop
- Long-term hepatic follow-up for those with significant liver injury

Poison Control / Emergency Assistance:

Contact Emergency Services Immediately:

- **USA**: Poison Control (1-800-222-1222) or 911 Emergency Services
- **EU (UK)**: National Poisons Information Service (0844-892-0111) or Emergency (999)
- **India**: National Poison Information Centre (Delhi - 011-4060-6060) or Local Emergency

Information to Provide:

- Exact number of sachets ingested
- Approximate time of ingestion
- Patient age, weight, medical conditions
- Current medications
- Time and date of contact

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Therapeutic Mechanism of Action:

ComfortCold Plus™ is a combination product containing four synergistic active pharmaceutical ingredients, each with distinct pharmacological properties targeting different aspects of upper respiratory tract infection symptomatology.

Individual Component Pharmacodynamics:

1. Acetaminophen (Paracetamol) - Analgesic/Antipyretic

Mechanism of Action:

- Inhibition of prostaglandin synthesis in the central nervous system (hypothalamus)
- Selective inhibition of cyclooxygenase (COX) enzymes, primarily COX-3 and COX-2 in brain tissue

- Elevation of pain threshold in the central nervous system
- Suppression of hypothalamic thermogenic center; direct effect on temperature regulation

Pharmacological Effects:

- **Analgesia**: Effective for mild to moderate pain (headache, body aches, sore throat) with onset 30-60 minutes
- **Antipyresis**: Reduces elevated body temperature through central hypothalamic action; fever reduction observable within 30-45 minutes
- **Anti-inflammatory**: Minimal; acetaminophen is NOT considered a true NSAID
- **Duration**: 4-6 hours per dose; peak effect 1-2 hours post-administration

Pharmacological Selectivity:

- More selective for CNS COX inhibition than peripheral COX inhibition
- Does not significantly inhibit platelet aggregation
- Lacks significant anti-inflammatory activity compared to NSAIDs
- Advantage over NSAIDs: Lower risk of gastrointestinal bleeding and renal toxicity

2. Dextromethorphan Hydrobromide (DXM) - Antitussive

Mechanism of Action:

- Non-narcotic, non-analgesic cough suppressant
- Antagonism of N-methyl-D-aspartate (NMDA) receptors in the brain stem cough center (nucleus tractus solitarius)
- Elevation of cough threshold by 10-30% depending on dose
- Central nervous system depressant effects; mild analgesic properties (unrelated to cough suppression)

Pharmacological Effects:

- **Antitussive Efficacy**: Effective for nonproductive cough with onset 15-30 minutes; equivalent to low-dose codeine (15-20 mg)
- **Duration**: 3-6 hours per dose
- **Selectivity**: Limited selectivity for cough center; CNS effects occur at higher plasma concentrations
- **Potency**: 10-30 mg range produces significant cough suppression without marked CNS depression at therapeutic doses
- **Clinical Note**: Less effective for productive (wet) cough; ideal for dry, irritative cough associated with viral upper respiratory infections

Neurochemical Interactions:

- Interaction with sigma receptors (may have neuroprotective properties)
- Weak monoamine reuptake inhibition
- NMDA receptor antagonism shared mechanism with dissociative anesthetics

3. Phenylephrine Hydrochloride - Nasal Decongestant

Mechanism of Action:

- Selective alpha-1-adrenergic receptor agonist (post-synaptic)
- Vasoconstriction of nasal mucosa vasculature through activation of alpha-1-adrenergic receptors
- Reduced blood flow and interstitial edema in nasal turbinates and paranasal sinuses
- Decreased mucus production through reduced vascular permeability

Pharmacological Effects:

- **Decongestant Efficacy**: Rapid nasal decongestion with onset 15-30 minutes; duration 4-6 hours
- **Mechanism Specificity**: Alpha-1 selectivity (low affinity for beta-receptors)
- **Systemic Effects**: Mild systemic vasoconstriction; minimal cardioselective beta-receptor activity
- **Potential Adverse Effects**: Transient hypertension, reflex bradycardia possible (though less than with non-selective alpha agonists)
- **Rebound Congestion**: Minimal risk with short-term use (5 days); rebound phenomenon typically associated with intranasal forms and prolonged use >7 days

Hemodynamic Changes:

- Increases peripheral vascular resistance
- May cause slight elevation in blood pressure (typically 5-10 mmHg systolic)
- Weak reflexive bradycardia may occur as compensatory mechanism
- Maintains nasal mucosal blood flow while reducing edema

4. Chlorpheniramine Maleate - Antihistamine (First-Generation, Sedating)

Mechanism of Action:

- Competitive antagonism of histamine H1 receptors on tissues and cells
- Blocks histamine-mediated effects: vasodilation, increased vascular permeability, smooth muscle contraction
- Reduction of allergic symptomatology: sneezing, rhinorrhea (runny nose), ocular pruritus
- Significant anticholinergic activity due to H1 antagonist structure
- Central nervous system penetration; crosses blood-brain barrier readily (lipophilic)

Pharmacological Effects:

- **Antihistamine Efficacy**: Effective for allergic rhinitis, sneezing, and rhinorrhea; onset 15-30 minutes
- **Duration**: 4-6 hours per dose
- **Anticholinergic Effects**: Dry mouth, mild bronchodilation, mydriasis, reduced lacrimation (may worsen dry eye)
- **Sedation**: Marked central H1 receptor antagonism; significant drowsiness (feature of first-generation antihistamines)
- **Selectivity**: Non-selective for H1 receptor subtypes; crosses blood-brain barrier
- **Potency**: Intermediate potency antihistamine; more potent than diphenhydramine but less sedating

Neurochemical Interactions:

- Inhibition of monoamine oxidase (minor activity)
- Antimuscarinic (anticholinergic) properties
- Potential serotonergic effects at higher doses
- May have mild antiemetic properties (mechanism unclear)

Combination Pharmacodynamic Synergy:

The four-component formulation targets multiple pathways in upper respiratory infection symptomatology:

Symptom	Acetaminophen	DXM	Phenylephrine	Chlorpheniramine
Fever	***	-	-	-
Headache/Body Ache	***	-	-	-
Cough	-	***	-	-
Nasal Congestion	-	-	***	-
Sneezing/Rhinorrhea	-	-	-	***
Sore Throat	***	**	-	-
Itchy Eyes	-	-	-	***
General Malaise	**	-	-	-

Table 2: Symptom Coverage by Active Ingredient (* = primary effect, ** = secondary effect, *** = major effect)

Receptor Binding and Pharmacological Selectivity:

- **Acetaminophen**: COX-1, COX-2, COX-3 inhibition (central predominance)
- **DXM**: NMDA receptor antagonism, sigma receptor agonism, monoamine reuptake inhibition
- **Phenylephrine**: Alpha-1-adrenergic receptor agonism (high selectivity; minimal beta effects)
- **Chlorpheniramine**: H1-histamine receptor antagonism, muscarinic cholinergic receptor antagonism

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5.2 Pharmacokinetic Properties

Absorption:

Acetaminophen:

- **Route**: Oral (via GI tract after sachet dissolution in water)
- **Absorption Site**: Primarily small intestine (duodenum and jejunum); some gastric absorption
- **Bioavailability**: 85-95% (accounting for minimal first-pass metabolism)
- **Time to Peak Plasma Concentration (Tmax)**: 30-120 minutes (median ~60 minutes)
- **Peak Plasma Concentration (Cmax)**: 5-20 mcg/mL with standard 325 mg dose
- **Factors Affecting Absorption**:
    - Food: Minimal effect on extent of absorption; may delay Tmax by 10-20 minutes
    - pH: Absorbs well across pH range; solubilized formulation (sachet) enhances absorption
    - Gastric motility: Rapid transit enhances absorption; delayed gastric emptying decreases rate
    - Formulation: Powder/solution formulation (sachet) shows faster absorption than solid tablets

Dextromethorphan Hydrobromide:

- **Route**: Oral (via GI tract)
- **Absorption**: Rapidly and completely absorbed from small intestine
- **Bioavailability**: 10-20% due to substantial first-pass hepatic metabolism (CYP2D6, CYP3A4)
- **Tmax**: 30-120 minutes (median ~60 minutes)
- **Cmax**: 5-30 ng/mL with standard 10 mg dose
- **Saturable Metabolism**: At higher doses, first-pass metabolism becomes partially saturated, leading to disproportionate increase in systemic exposure

Phenylephrine Hydrochloride:

- **Route**: Oral (via GI tract)
- **Absorption**: Rapidly absorbed from small intestine
- **Bioavailability**: 15-25% (significant first-pass hepatic metabolism via monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT))
- **Tmax**: 20-60 minutes (median ~45 minutes)
- **Cmax**: 0.5-2 ng/mL with standard 5 mg dose
- **Stability**: Unstable in acidic gastric medium; protected by sachet formulation ensuring GI delivery
- **Effect of Food**: May reduce bioavailability; absorbed better on empty stomach or with water

Chlorpheniramine Maleate:

- **Route**: Oral (via GI tract)
- **Absorption**: Rapidly and completely absorbed from GI tract
- **Bioavailability**: 40-50% (first-pass hepatic metabolism via CYP3A4, CYP2D6)
- **Tmax**: 30-120 minutes (median ~60 minutes)
- **Cmax**: 0.5-3 ng/mL with standard 2 mg dose
- **Lipophilicity**: Highly lipophilic; penetrates blood-brain barrier readily
- **Protein Binding**: 70-80%; significant plasma protein binding

Distribution:

Acetaminophen:

- **Volume of Distribution (Vd)**: 0.8-1.0 L/kg
- **Protein Binding**: 10-25% (low protein binding)
- **Tissue Distribution**: Distributes widely throughout body water compartments
- **CNS Penetration**: Moderate penetration of blood-brain barrier due to moderate lipophilicity
- **Placental Transfer**: Crosses placenta; fetal:maternal ratio ~0.8-1.0 (clinically relevant in pregnancy)
- **Breast Milk**: Excreted in breast milk; infant dose approximately 1-2% of maternal dose
- **Biological Half-Life**: 2-3 hours (therapeutic range)

Dextromethorphan:

- **Volume of Distribution (Vd)**: 5-7 L/kg (extensive tissue distribution)
- **Protein Binding**: 40-50%
- **CNS Penetration**: High lipophilicity; readily crosses blood-brain barrier; concentrates in brain tissues
- **Tissue Distribution**: Distributes extensively; particular affinity for lung and brain tissue
- **Metabolite (Dextrorphan)**: Significant CNS penetration; may contribute to pharmacological effects
- **Biological Half-Life**: 11-16 hours for DXM; 31-33 hours for active metabolite dextrorphan

Phenylephrine:

- **Volume of Distribution (Vd)**: 0.5-0.7 L/kg
- **Protein Binding**: Minimal protein binding expected
- **Tissue Distribution**: Distributes to vascular tissue, heart, CNS (minimal)
- **CNS Penetration**: Poor CNS penetration due to hydrophilicity and limited BBB permeability
- **Vascular Localization**: Preferential distribution to vascular smooth muscle of nasal mucosa and systemic vasculature
- **Biological Half-Life**: 2.5-3 hours

Chlorpheniramine:

- **Volume of Distribution (Vd)**: 10-16 L/kg (extensive tissue distribution)
- **Protein Binding**: 70-80%
- **CNS Penetration**: High lipophilicity; readily crosses blood-brain barrier
- **Tissue Distribution**: Distributes widely; particularly concentrates in CNS, heart, lung tissue
- **Tissue Half-Life**: Longer in tissues than plasma (24-48 hours in some tissues)
- **Biological Half-Life**: 12-18 hours (longer than DXM)

Metabolism:

Acetaminophen:

- **Primary Metabolic Pathway**: Phase II conjugation reactions (glucuronidation and sulfation)
    - **Glucuronidation**: Catalyzed by UDP-glucuronosyltransferase (UGT) enzymes; accounts for 50-60% of metabolism
    - **Sulfation**: Catalyzed by sulfotransferase (SULT) enzymes; accounts for 25-35% of metabolism
    - **Oxidative Metabolism**: Minor pathway via CYP2E1 and CYP1A2; produces toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI)
- **Detoxification**: NAPQI is rapidly conjugated with hepatic glutathione; becomes non-toxic
- **Toxic Threshold**: When glutathione stores become depleted (typically >4 g/day acetaminophen), NAPQI accumulates and causes hepatocellular necrosis
- **Genetic Polymorphisms**: UGT1A1 and SULT1A1 variants may affect acetaminophen metabolism; individuals with reduced glucuronidation capacity at higher risk for toxicity

- **Enzyme Induction/Inhibition**:
    - Alcohol: Induces CYP2E1; increases NAPQI production; increases hepatotoxicity risk
    - NSAIDs: May compete for sulfation pathways
    - Warfarin: No significant interaction at therapeutic doses

Dextromethorphan:

- **Primary Metabolic Pathway**: N-demethylation via CYP2D6
    - CYP2D6 is the major enzyme responsible for converting DXM to dextrorphan (active metabolite)
    - Secondary pathways: CYP3A4, CYP1A2 (minor contribution)
- **Active Metabolite**: Dextrorphan produced is pharmacologically active; further metabolized by glucuronidation and sulfation
- **Genetic Polymorphisms**: CYP2D6 genotype significantly affects DXM metabolism
    - Poor metabolizers: Accumulate DXM; prolonged plasma levels; increased CNS effects
    - Extensive metabolizers: Rapid metabolism; standard pharmacokinetics
    - Ultra-rapid metabolizers: Enhanced dextrorphan production; may have augmented effects
- **Drug Interactions**: Substrates and inhibitors of CYP2D6 (SSRIs, quinidine, methadone) compete for metabolism
- **First-Pass Effect**: Saturable metabolism; non-linear kinetics at higher doses

Phenylephrine:

- **Primary Metabolic Pathways**:
    - **Monoamine Oxidase (MAO)**: Primary enzyme; metabolizes catecholamine side chain
    - **Catechol-O-methyltransferase (COMT)**: Secondary pathway; methylates catechol moiety
    - **Aldehyde and Alcohol Dehydrogenases**: Minor contributions
- **Metabolites**: Produces inactive metabolites
- **Hepatic and Extra-hepatic Metabolism**: Metabolized systemically, not solely by liver; contributes to low bioavailability
- **Drug Interactions**: MAOIs block metabolism; severe hypertension risk (contraindicated)
- **Genetic Polymorphisms**: COMT Val158Met polymorphism may affect metabolism

Chlorpheniramine:

- **Primary Metabolic Pathway**: Hepatic metabolism via CYP3A4 and CYP2D6
    - N-demethylation to form desmethylchlorpheniramine (active metabolite)
    - Further conjugation with glucuronic acid and sulfate
- **Active Metabolites**: Desmethylchlorpheniramine is pharmacologically active; contributes to prolonged antihistamine effects

- **Genetic Polymorphisms**: CYP2D6 and CYP3A4 variants may affect metabolism
- **Drug Interactions**: CYP3A4 and CYP2D6 inhibitors (ketoconazole, SSRIs) may increase chlorpheniramine levels

Elimination:

Acetaminophen:

- **Route**: Primarily urinary (renal excretion of conjugate metabolites)
- **Percentage Eliminated**: >95% excreted as conjugated metabolites in urine within 24 hours
- **Elimination Half-Life**: 2-3 hours (terminal elimination phase)
- **Renal Clearance**: Requires normal renal function for efficient elimination
- **Hepatic Impairment**: Prolongs half-life and increases toxicity risk

Dextromethorphan:

- **Route**: Primarily urinary
- **Percentage Eliminated**: >95% of metabolites excreted in urine; <5% excreted unchanged
- **Elimination Half-Life**: 11-16 hours for DXM; 31-33 hours for active metabolite dextrorphan
- **Biliary Excretion**: Minimal
- **Cumulative Effects**: Prolonged half-life may lead to accumulation with repeated dosing in some individuals

Phenylephrine:

- **Route**: Primarily urinary
- **Percentage Eliminated**: <5% excreted unchanged; majority as metabolites
- **Elimination Half-Life**: 2.5-3 hours
- **Biliary Excretion**: Minimal
- **Rapid Clearance**: High hepatic extraction ratio; rapidly cleared from circulation

Chlorpheniramine:

- **Route**: Primarily urinary
- **Percentage Eliminated**: 30-50% excreted unchanged; 50-70% as metabolites
- **Elimination Half-Life**: 12-18 hours (significantly longer than dextromethorphan and phenylephrine)
- **Potential for Accumulation**: Prolonged half-life may lead to accumulation with repeated dosing
- **Biliary Excretion**: Minimal; primarily renal

Special Population Pharmacokinetics:

Renal Impairment:

- **Acetaminophen**: eGFR <30 mL/min may prolong half-life; standard dose acceptable but dose interval should be increased
- **Dextromethorphan**: Clearance reduced; consider dose reduction in severe renal impairment

- **Phenylephrine**: Metabolism not significantly affected by renal function; no dose adjustment typically needed
- **Chlorpheniramine**: Clearance reduced; half-life prolonged; consider dose reduction in severe renal impairment

Hepatic Impairment:

- **Acetaminophen**: Greatest concern; contraindicated in severe cirrhosis; dose reduction in Child-Pugh B
- **Dextromethorphan**: Metabolism impaired; accumulation risk; consider dose reduction
- **Phenylephrine**: Hepatic metabolism via MAO/COMT; function generally preserved in hepatic disease
- **Chlorpheniramine**: Metabolism reduced; consider dose reduction in significant hepatic impairment

Age (Elderly >65 years):

- Combination of decreased hepatic metabolism, reduced renal clearance, and decreased body water
- Increased sensitivity to anticholinergic effects of chlorpheniramine
- Potential for accumulation with repeated dosing
- Dose reduction may be appropriate in frail elderly

Pediatric Patients (<12 years):

- Slower metabolic clearance of all components
- Enhanced susceptibility to anticholinergic effects of chlorpheniramine
- Risk of dextromethorphan toxicity at standard adult doses
- Product not indicated for this age group

5.3 Preclinical Safety Data (Non-Clinical Studies)

Acute Toxicity Studies:

Acetaminophen:

- **LD50 (Oral, Rat)**: 375-500 mg/kg
- **LD50 (Oral, Mouse)**: 254-338 mg/kg
- **LD50 (IV, Rat)**: 236 mg/kg
- **Clinical Relevance**: Therapeutic index approximately 100-150 fold; toxicity predominantly via metabolite NAPQI

Dextromethorphan Hydrobromide:

- **LD50 (Oral, Rat)**: 140-260 mg/kg
- **LD50 (IV, Rat)**: 28-40 mg/kg
- **Clinical Relevance**: Central toxicity at high doses; respiratory depression, seizures

Phenylephrine Hydrochloride:

- **LD50 (Oral, Rat)**: 97 mg/kg
- **LD50 (IV, Rat)**: 7.5 mg/kg
- **LD50 (SC, Rat)**: 24 mg/kg
- **Clinical Relevance**: Marked differences between routes; systemic toxicity due to sympathomimetic overdrive

Chlorpheniramine Maleate:

- **LD50 (Oral, Mouse)**: 300-400 mg/kg
- **LD50 (Oral, Rat)**: 180-220 mg/kg
- **LD50 (IV, Mouse)**: 22-31 mg/kg
- **Clinical Relevance**: Central toxicity predominates; anticholinergic crisis at high doses

Subacute and Chronic Toxicity:

Acetaminophen (90-day oral study, Rat):

- NOAEL (No Observed Adverse Effect Level): 300 mg/kg/day (approximately 24-fold the clinical dose)
- LOAEL (Lowest Observed Adverse Effect Level): 600 mg/kg/day (elevated liver enzymes, hepatic necrosis at 1500 mg/kg/day)
- Target organs: Liver (hepatotoxicity at high doses)

Dextromethorphan (13-week oral study, Rat):

- NOAEL: 80 mg/kg/day (approximately 200-fold the clinical dose)
- LOAEL: 160 mg/kg/day (CNS effects, reduced body weight gain)
- Target organs: Brain/CNS

Phenylephrine (13-week oral study, Rat):

- NOAEL: 25 mg/kg/day (approximately 100-fold the clinical dose)
- LOAEL: 50 mg/kg/day (cardiovascular effects, blood pressure elevation)
- Target organs: Cardiovascular system

Chlorpheniramine (90-day oral study, Rat):

- NOAEL: 40 mg/kg/day (approximately 400-fold the clinical dose)
- LOAEL: 80 mg/kg/day (CNS effects, increased liver weight)
- Target organs: CNS, liver

Genotoxicity (Mutagenicity) Studies:

Acetaminophen:

- **Ames Test**: Negative (non-mutagenic in bacterial systems)
- **In Vitro Micronucleus Test**: Negative
- **In Vivo Micronucleus Test (Rat)**: Negative at doses up to 500 mg/kg
- **Conclusion**: No genotoxic potential

Dextromethorphan:

- **Ames Test**: Negative
- **In Vitro Chromosomal Aberration**: Negative
- **Conclusion**: No significant genotoxic potential

Phenylephrine:

- **Ames Test**: Negative
- **Conclusion**: No genotoxic potential reported

Chlorpheniramine:

- **Ames Test**: Negative
- **In Vitro Micronucleus**: Negative
- **Conclusion**: No genotoxic potential

Carcinogenicity Studies:

Acetaminophen:

- **Rat (2-year study)**: No treatment-related neoplasias at doses up to 300 mg/kg/day
- **Mouse (2-year study)**: No treatment-related neoplasias at doses up to 750 mg/kg/day
- **Conclusion**: No carcinogenic potential in animal models
- **Note**: Increased hepatotoxicity at high chronic doses; risk of hepatocellular adenoma secondary to chronic hepatotoxicity/regeneration

Other Components (Dextromethorphan, Phenylephrine, Chlorpheniramine):

- **Comprehensive Carcinogenicity Data**: Limited formal long-term carcinogenicity studies
- **Assessment**: Based on available short-term/subacute data, no obvious carcinogenic alerts

Reproductive and Developmental Toxicity:

Acetaminophen:

- **Fertility**: No adverse effects on male or female fertility in rat studies at doses up to 300 mg/kg/day
- **Developmental**: No teratogenic effects in rat and rabbit studies; NOAEL >500 mg/kg/day
- **Embryotoxicity**: No significant embryonic/fetal toxicity
- **Lactation**: No adverse effects on offspring during nursing

Dextromethorphan:

- **Fertility**: Limited data; no specific adverse effects reported
- **Developmental**: Rabbit teratology studies negative at doses up to 350 mg/kg/day
- **Conclusion**: No teratogenic potential at therapeutic doses

Phenylephrine:

- **Fertility**: No specific adverse effects on male or female reproductive performance
- **Developmental**: Rabbit studies show no teratogenic effects at doses up to 50 mg/kg/day

- **Potential Concern**: Sympathomimetic activity may theoretically affect placental blood flow at very high doses; not substantiated in animal studies

Chlorpheniramine:

- **Fertility**: No adverse effects on fertility parameters in rat studies
- **Developmental**: Rat and rabbit teratology studies negative at doses up to 100 mg/kg/day
- **Lactation**: No adverse effects on nursing pups at therapeutic maternal doses

Overall Reproductive Assessment: No significant reproductive or developmental toxicity concerns identified at therapeutic doses.

Local Tolerance (Irritation) Studies:

Oral/Gastrointestinal Mucosa:

- Sachet formulation designed for dissolution in water; minimal direct mucosal contact in dry form
- Once dissolved, formulation is well-tolerated by gastric and small intestinal mucosa
- No evidence of local irritation in animal studies
- Occasional nausea/gastrointestinal upset reflects pharmacological effects rather than local irritation

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

All Excipients Used in ComfortCold Plus™ Sachets:

Excipient Name	Qty/Sachet	Pharm. Std.	Function/Purpose
Citric Acid Anhydrous	800 mg	Ph.Eur./USP	Acidifying agent; effervescence promoter
Sodium Bicarbonate	650 mg	Ph.Eur./USP	Effervescent agent; pH modifier
Sodium Carbonate Anhydrous	450 mg	Ph.Eur./USP	Effervescent agent; solubility enhancer
Lactose Monohydrate	800 mg	Ph.Eur./USP	Diluent/filler; bulking agent
Microcrystalline Cellulose (Avicel PH101)	500 mg	Ph.Eur./USP	Suspending agent; flow improver
Croscarmellose Sodium	120 mg	Ph.Eur./USP	Disintegrant; dissolution aid
Magnesium Stearate	45 mg	Ph.Eur./USP	Lubricant; anti-caking agent
Silicon Dioxide (Colloidal)	80 mg	Ph.Eur./USP	Anti-caking agent; flow promoter
Aspartame	30 mg	Ph.Eur./USP	Sweetening agent; taste masker
Lemon Flavor (Natural & Synthetic)	60 mg	FCC/Ph.Eur.	Organoleptic agent; flavor
Menthol (L-Menthol)	25 mg	Ph.Eur./USP	Flavor; cooling sensation
Sucrose (Pulverized)	300 mg	Ph.Eur./USP	Sweetening agent; bulking agent
Acacia Gum (Gum Arabic)	45 mg	Ph.Eur./USP	Emulsifying agent; stabilizer
Ascorbic Acid (Vitamin C)	35 mg	Ph.Eur./USP	Antioxidant; preservative
Talc (Magnesium Silicate)	50 mg	Ph.Eur./USP	Flow agent; anti-caking
Sunset Yellow FCF (E110)	2 mg	Ph.Eur./USP	Coloring agent; visual identification
Saccharin Sodium	15 mg	Ph.Eur./USP	Intense sweetening agent

Table 3: Complete Excipient List with Quantity and Function

Excipients with Known Effects on Health:

According to regulatory guidelines, the following excipients have known effects and should be declared prominently:

1. **Lactose Monohydrate (800 mg/sachet)**:
    - Known Effect: May cause gastrointestinal symptoms in patients with lactose intolerance or malabsorption
    - Risk Assessment: Patients with confirmed lactose intolerance should use alternative products
    - Clinical Impact: May exacerbate existing gastrointestinal symptoms; diarrhea possible
2. **Aspartame (30 mg/sachet)**:
    - Known Effect: Contains phenylalanine (approximately 10 mg per sachet equivalent)
    - Risk Assessment: Contraindicated in phenylketonuria (PKU); must inform patients with PKU not to use
    - Clinical Impact: CNS damage possible if PKU patients consume product
3. **Sodium Content (Total ~245 mg/sachet)**:
    - Known Effect: 10.6% of WHO recommended maximum daily intake per sachet
    - Equivalent to approximately 0.6 g sodium chloride (as sodium ions from sodium bicarbonate, sodium carbonate, saccharin sodium, sodium citrate)
    - Risk Assessment: Patients on sodium-restricted diet (acute heart failure, hypertension, renal disease) should limit use
    - Clinical Impact: May worsen fluid retention, hypertension in susceptible patients
4. **Sucrose (300 mg/sachet)**:
    - Known Effect: Fermentable carbohydrate; may cause gastrointestinal discomfort in sensitive individuals
    - Risk Assessment: Patients with hereditary fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should avoid
    - Clinical Impact: Abdominal cramping, bloating, diarrhea possible
5. **Sunset Yellow FCF/E110 (2 mg/sachet)**:
    - Known Effect: Azo dye; rare risk of hypersensitivity reactions
    - Risk Assessment: Patients with food dye sensitivity or aspirin sensitivity may react
    - Clinical Impact: Urticaria, angioedema, anaphylaxis (rare)

6.2 Incompatibilities

Stability and Incompatibility Assessment:

The powder formulation in sachets is designed for stability and minimal incompatibilities. However, the following should be noted:

Chemical Incompatibilities (In Dry Formulation):

- **Acetaminophen + Moisture**: Degradation pathway involves hydrolysis; moisture should be <2% to prevent degradation
- **Citric Acid + Sodium Bicarbonate**: Effervescent reaction occurs only when dissolved in water; dry powder is stable due to moisture exclusion
- **Phenylephrine**: Sensitive to oxidation; ascorbic acid (antioxidant) included in formulation to prevent degradation

Post-Dissolution Interactions (In Aqueous Solution):

- **pH Stability**: Once dissolved in water, solution becomes basic (pH ~7.5-8.0) due to sodium carbonate/bicarbonate
- **Time Stability**: Prepared solution should be consumed immediately; prolonged storage (>30 minutes) may lead to:
    - Acetaminophen: Minimal degradation within 30 minutes
    - Dextromethorphan: Stable in aqueous solution
    - Phenylephrine: May oxidize over time; color change possible (slight browning)
    - Chlorpheniramine: Stable in aqueous solution

Incompatibilities with Other Medications (Drug-Drug):
See Section 4.5 for detailed drug interaction information.

Incompatibilities with Food/Beverages:

- **Alcohol**: Avoid concurrent consumption (hepatotoxicity risk with acetaminophen, enhanced CNS depression)
- **Acidic Beverages**: Do not dissolve in acidic beverages (orange juice, cola); phenylephrine stability compromised
- **Milk Products**: Dissolution slightly delayed but pharmacologically equivalent; not contraindicated

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6.3 Shelf Life

Storage Stability Data (Stability Studies):

Accelerated Stability Study (40°C ± 2°C / 75% RH ± 5%):

- Duration: 6 months
- Findings: Acceptable changes in content (±5% allowed per ICH Q1A guidance)
    - Acetaminophen: 99-101% of labeled content
    - Dextromethorphan HBr: 98-102% of labeled content
    - Phenylephrine HCl: 96-100% of labeled content (slight oxidation)
    - Chlorpheniramine Maleate: 99-101% of labeled content
- Conclusion: Accelerated conditions demonstrate stability; extrapolation supports 24-36 month shelf life at 25°C/60% RH

Long-Term Stability Study (25°C ± 2°C / 60% RH ± 5%):

- Duration: 36 months (ongoing; 24-month data complete and supports claims)

- 24-Month Data:
    - All active ingredients: 99-102% of labeled content
    - Appearance: No discoloration; white to off-white color maintained
    - Dissolution: Meets specifications (complete dissolution in ≤3 minutes)
    - Moisture: <2% (specification limit)

Photostability Study (ICH Option 1):

- Sachets exposed to 1.2 million lux.hours and 200 W.h/m² UV light
- Assessment: Minimal color change; active ingredients stable
- Conclusion: Packaging (opaque aluminum/paper sachet) provides adequate light protection

Proposed Shelf Life:

- **Unopened Sachets in Original Packaging**: 36 months at 25°C/60% RH
- **Opened Sachet (Prepared Solution)**: Consume within 30 minutes
- **Storage Conditions**: "Store below 25°C in a dry place; protect from light and moisture"

6.4 Nature and Contents of Container

Primary Packaging:

Sachet Composition (Blister Strip):

- **Material**: Aluminum/Aluminum (Al/Al) composite laminate with paper backing
    - Outer Layer: White kraft paper with print (product name, dosage, batch number, expiry)
    - Middle Layer: Aluminum foil (18-20 micrometer thickness)
    - Inner Layer: Aluminum foil laminate with moisture barrier
- **Specifications**:
    - Thickness: 60-80 micrometer total
    - Tear Strength: ≥50 N/15mm (allows easy opening)
    - Moisture Transmission Rate: <0.5 mg/24h/100cm² (protects from humidity)
    - Oxygen Transmission Rate: <1 cm³/24h/100cm² (protects from oxidation)
    - Opacity: ≥95% (light protection)
- **Dimensions**:
    - Individual Sachet: 90 mm L × 65 mm W (when sealed)
    - Weight (Gross): 5.5 grams of powder content
    - Printing: Black offset printing with product information, batch code, expiry date

Secondary Packaging (Outer Box):

- **Material**: Corrugated cardboard (C-flute, white bleached kraft)
- **Box Dimensions**: 120 mm W × 85 mm D × 125 mm H (for 10-sachet pack)

- **Printing**: 4-color lithographic print containing:
  - Product Name: ComfortCold Plus™
  - Strength: 325 mg / 10 mg / 5 mg / 2 mg Sachets
  - Route of Administration: Oral, for dissolution in water
  - Manufacturer: PharmaCare Laboratories Pvt. Ltd., EU/India
  - Regulatory Information: SMPC reference number, batch/lot number, expiry date
  - Storage Instructions: "Store below 25°C in a dry place"
  - Directions: "Dissolve one sachet in 200 mL hot water; do not exceed 4 sachets in 24 hours"

Pack Sizes:

- **10 Sachets per box** (standard consumer pack)
- **5 Sachets per box** (compact/trial pack)
- **50 Sachets per box** (institutional/hospital pack)
- **100 Sachets per box** (bulk professional pack)

Child-Resistant Closure:

- Individual sachets have easy-tear perforated edge (not child-resistant by nature)
- Outer box designed with child-safety considerations
- **Label Requirements**: "Keep out of reach of children" clearly marked on packaging

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6.5 Storage Conditions

Storage Instructions (Critical for Product Stability):

Temperature:

- **Primary Storage**: Below 25°C (room temperature)
- **Not to exceed**: 30°C for extended periods
- **Avoidance**: Do not refrigerate or freeze (may cause condensation and moisture ingress when removed to room temperature)
- **Pharmacy Setting**: Store in climate-controlled section; temperature monitoring recommended

Humidity:

- **Target Relative Humidity**: 45-60% (optimal)
- **Maximum Relative Humidity**: <65% RH
- **Risk**: Exposure to >70% RH for extended periods may increase moisture content >2% and lead to:
  - Acetaminophen degradation (increased impurities)
  - Caking/clumping of powder
  - Accelerated dissolution of sachet integrity
  - Phenylephrine oxidation (discoloration)

Light Protection:

- **Requirement**: Protect from direct sunlight and strong artificial light
- **Packaging**: Aluminum/paper composite provides adequate light protection when intact
- **Display**: If dispensing from bulk container, transfer to light-protected cabinet
- **Risk of Exposure**: Prolonged light exposure may cause slight yellowing of powder (harmless but signals quality issue)

Physical Conditions:

- **Separation from Chemicals**: Store away from perfumes, cosmetics, volatile organic compounds
- **Ventilation**: Adequate air circulation to prevent moisture accumulation
- **Storage Location Examples**:
  - Pharmacy: Locked medication cabinet with humidity/temperature control
  - Home: Bathroom medicine cabinet (above toilet to avoid splash) or bedroom closet (cool, dry location)
  - Institutions**: Hospital pharmacy with controlled environment

Opened Sachet:

- Once sachet is opened/torn, transfer entire contents to water immediately
- Do not re-seal sachet or store opened powder
- Unused prepared solution should NOT be stored; discard after 30 minutes

Disposal Conditions:

- Do not pour unused medication down sink or toilet
- Utilize community drug take-back programs where available
- If unavailable, mix medication with unpalatable substance (coffee grounds, cat litter) in plastic bag before placing in household trash

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6.6 Special Precautions for Disposal

Environmental and Regulatory Considerations:

Disposal of Unused/Expired Sachets:

Recommended Disposal Methods (In Order of Preference):

1. **Community Drug Take-Back Programs** (Most Preferred):
   - Contact local pharmacy (most participate)
   - Contact local government waste management facilities
   - Many hospitals/clinics offer take-back programs
   - Disposal is safe, environmentally responsible, and confidential
2. **Home Disposal** (If Take-Back Unavailable):
   - Mixture Method: Add sachets/powder to unpalatable substance (coffee grounds, used cat litter, salt, flour) in sealable plastic bag to reduce palatability and prevent accidental ingestion

- Placement: Place sealed bag in household trash (not recycling bin)
- Purpose: Rendering medication unpalatable prevents accidental ingestion by children/pets; reduces water contamination risk

3. **Specific Instructions Not Recommended** (To Avoid Environmental Contamination):
    - **Do NOT flush down toilet or pour down sink/drain**: Risk of water contamination; municipal water treatment plants may not completely remove pharmaceutical residues; aquatic organism toxicity possible
    - **Do NOT place loose sachets in trash**: Risk of environmental contamination; child/pet ingestion risk
    - **Do NOT place in recycling bin**: Contaminates recycling streams; non-recyclable due to chemical content

Environmental Impact Considerations:

- Acetaminophen, dextromethorphan, phenylephrine, and chlorpheniramine have been detected in aquatic environments
- Even at low concentrations, prolonged exposure may affect aquatic organisms (fish feminization, behavioral changes with DXM)
- Proper disposal minimizes environmental burden

Regulatory Compliance:

- Disposal should comply with local pharmaceutical waste regulations
- Healthcare facilities subject to stricter regulations; must use licensed medical waste disposal contractors
- Individuals should follow FDA or EMA guidelines for household medication disposal

Special Circumstances:

- **Pet/Child Accidental Ingestion**: Do not induce vomiting; call Poison Control immediately (USA: 1-800-222-1222)
- **Medication Recall**: Follow specific disposal instructions from manufacturer; return via pharmacy if possible
- **Bulk Disposal** (Healthcare Facilities): Use licensed pharmaceutical waste contractor; incineration recommended (destroys active ingredients completely)

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7. MARKETING AUTHORIZATION HOLDER & MANUFACTURER INFORMATION

7.1 Marketing Authorization Holder

Company Name: **PharmaCare Laboratories Pvt. Ltd.**

Registration Status: EU Pharmaceutical Company (Authorized Distributor in European Union)

Registered Address (EU Distribution Center):
PharmaCare Laboratories European Division
Pharmastrasse 42
1020 Vienna
Austria

Regulatory Contact:

- Regulatory Affairs Manager: Dr. Elisabeth Weber
- Email: regulatory@pharmacare-eu.com
- Phone: +43 1 2345 6789

Product Registration Numbers:

- **EU Registration (via National Procedure)**: ComfortCold Plus™ - EMEA/CHMP/EEA Authorization Pending/Granted*
- **EMA Reference Number**: EMEA/CHMP/529862
- **National Competent Authority**: Austrian Federal Office for Safety in Health Care (BASG/AGES)

7.2 Manufacturer Information

Primary Manufacturing Facility:

PharmaCare Laboratories Pvt. Ltd.
PharmaCare Laboratories European Division
Pharmastrasse 42
1020 Vienna
Austria

WHO-GMP Status: WHO-GMP Certified (Manufacturing Facility Compliant with WHO Good Manufacturing Practice Standards)

Certifications & Approvals:

- **ISO 9001:2015**: Quality Management System Certification
- **ISO 13485:2016**: Medical Device Quality Management (applicable components)
- **WHO-GMP Certificate**: Issued by Ministry of Health & Family Welfare, India (Valid: 2022-2027)
- **FDA Establishment License**: FDA Facility Identifier (FEI): [Assigned by FDA upon inspection]
- **EU Manufacturing Authorization**: Compliance with EudraLex Volume 4 (EU GMP Guidelines)

Facility Capabilities:

- **Equipment**: Modern tablet compression, powder blending, sacheting machinery (Bosch Packaging Technology)
- **Quality Control**: In-house analytical laboratory with HPLC, UV-VIS spectrophotometry, dissolution testing
- **Capacity**: 50 million sachets per annum (current capacity), expandable to 100 million
- **Clean Room Classification**: Grade C/D (ISO 14644 Classification 7/8)

Manufacturing Processes:

1. **Powder Blending**: Active pharmaceutical ingredients blended with excipients in geometric dilution to ensure homogeneity
2. **Sieving**: Sieve through #30 mesh to ensure uniform particle size
3. **Sachet Filling**: Automatic sachet filling and sealing machinery (Bausch & Strobel model)

4. **Packaging**: Individual sachets packed in cardboard boxes with appropriate labeling
5. **Quality Assurance**: Each batch undergoes in-process controls and finished product testing

Manufacturing Operations Manager:

- Name: Mr. Rajesh Patel
- Title: Senior Facility Manager, PharmaCare Labs Manufacturing
- Email: manufacturing@pharmacare-india.com
- Phone: +91 265 2563 2563

7.3 European Union Authorized Representative (EAR)

Name: **PharmaCare Europe GmbH**

Location: **Frankfurt am Main, Germany**

Address:
PharmaCare Europe GmbH
Pharmaceutical Regulatory Office
Mainzer Strasse 120
60311 Frankfurt am Main
Germany

Authorized Representative Contact:

- Director of Regulatory Affairs: Dr. Klaus Hoffmann, Ph.D.
- Email: ear@pharmacare-eu.de
- Phone: +49 69 96 75 2468

Responsibilities:

- Representation with European Medicines Agency (EMA)
- Correspondence with National Competent Authorities
- Quality defect reporting and adverse event handling for EU region
- Responsible for periodic safety updates (PSURs)

7.4 Quality Assurance and Regulatory Compliance

Quality Management System:

- **System**: Comprehensive QMS per ISO 9001:2015 and ICH Q10 guidelines
- **Documentation**: Standard Operating Procedures (SOPs) for manufacturing, testing, storage, distribution
- **Training**: Staff undergo initial and periodic training on GMP, product knowledge, quality procedures
- **Audits**: Internal audits quarterly; external audits by regulatory authorities as scheduled

Batch Release and Certificate of Analysis:

- Each batch of ComfortCold Plus™ Sachets undergoes comprehensive testing:
    - Identification tests (HPLC, TLC)
    - Assay (HPLC for each active ingredient)
    - Dissolution testing
    - Microbial contamination (aerobic/anaerobic, fungi, bacterial endotoxins)
    - Physical/chemical properties (moisture, appearance, pH of solution)
- Release criteria per ICH Q3B (Impurities in New Drug Substances and Products)
- Certificate of Analysis (CoA) provided with each batch shipment

Post-Market Surveillance:

- **Pharmacovigilance System**: Monitoring and reporting of adverse events
- **Adverse Event Reporting**: To regulatory authorities within specified timeframes
- **Product Complaints**: Investigation and root cause analysis for defects
- **Periodic Safety Update Reports (PSURs)**: Submitted per EMA/FDA requirements

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8. THERAPEUTIC INDICATIONS & CLINICAL USE

8.1 Approved Indications (Summary)

ComfortCold Plus™ Sachets are indicated for:

Symptomatic Relief of Upper Respiratory Tract Infection Symptoms:

- Common cold and influenza-like illness
- Cough (nonproductive, dry cough)
- Nasal congestion and sinus pressure
- Sneezing and rhinorrhea (runny nose)
- Headache and body aches associated with viral illness
- Sore throat discomfort
- Elevated body temperature (fever)
- Itchy and watery eyes (allergic symptoms)

Appropriate Patient Population: Adults and adolescents aged 16 years and older

Route of Administration: Oral (after dissolution in water)

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9. REGULATORY GUIDANCE & EVIDENCE BASE

9.1 Clinical Evidence Summary

Efficacy Evidence:
This product is formulated based on established clinical evidence for each component:

1. **Acetaminophen**: Decades of clinical use; efficacy for fever and pain well-established (multiple RCTs confirm efficacy)
2. **Dextromethorphan**: FDA-approved antitussive component; efficacy equivalent to low-dose codeine (15-20 mg)
3. **Phenylephrine**: FDA-approved nasal decongestant; onset 15-30 minutes; effective for symptomatic nasal congestion relief
4. **Chlorpheniramine**: First-generation antihistamine; FDA-approved; effective for allergic rhinitis symptoms

Combination Rationale: Synergistic targeting of multiple cold symptoms in single formulation enhances therapeutic convenience and compliance

9.2 Regulatory Pathway

Classification: Over-the-Counter (OTC) Medicinal Product (regulatory status varies by jurisdiction)

Regulatory Authority Approvals:

- **USA (FDA)**: GRAS status as combination product under OTC Drug Monograph or NDA (New Drug Application) pathway
- **EU**: Authorized via national procedure or decentralized procedure with EMA involvement
- **India**: Approved by Central Drugs Standard Control Organization (CDSCO); Schedule H classification

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10. CLINICAL SUMMARY & PATIENT INFORMATION

10.1 When to Use ComfortCold Plus™

Appropriate Use Cases:

- Acute viral upper respiratory infection with multiple symptoms
- Common cold with cough, congestion, fever, and allergic symptoms
- Influenza-like illness (for symptom management; does not treat infection)
- Allergic rhinitis with nasal congestion and sneezing

When NOT to Use:

- Productive cough with phlegm (use expectorant instead)
- Persistent cough >1 week (consult physician; may indicate serious condition)
- Persistent fever >3 days (consult physician; may indicate secondary bacterial infection)
- Severe underlying medical conditions (consult healthcare provider)

10.2 Patient Instructions Summary

Preparation and Dosing:

1. Dissolve one sachet in 200 mL hot water (60-80°C)
2. Stir for 30 seconds until completely dissolved
3. Allow to cool to comfortable drinking temperature

4. Drink immediately; do not store prepared solution
5. May repeat every 4-6 hours as needed
6. **Do NOT exceed 4 sachets per 24-hour period**
7. **Do NOT use for more than 5 consecutive days without medical consultation**

Important Cautions:

- May cause drowsiness; do not drive if drowsy
- Avoid alcohol (increases drowsiness and liver toxicity risk)
- Do not combine with other products containing acetaminophen
- Pregnant/breastfeeding: Consult doctor before use
- Stop use and consult doctor if: severe allergic reaction, persistent symptoms, worsening condition

10.3 Contact Information for Further Information

Patient Inquiries:

- **PharmaCare Customer Care**: 1-800-PHARMACY (toll-free in EU)
- **Email**: patientcare@pharmacare-eu.com
- **Website**: www.pharmacare-eu.com/products/comfortcold-plus

Healthcare Professional Inquiries:

- **Medical Information Department**: medicinfo@pharmacare-eu.com
- **Phone**: +43 1 2345 6790 (Austria, EU region)