

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Coldrex HotRem

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5.0 g sachet of powder for oral solution contains:

Active constituents:

Paracetamol	750.00 mg
Phenylephrine Hydrochloride	10.00 mg
Ascorbic acid	60.00 mg

Excipients with known effect:

Sucrose 2468.50 mg

Sodium 134.75 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for Oral Solution with honey and lemon flavor.

Sachet content: heterogeneous powder from off-white with beige shade to bright – brown, with white, bright-brown and dark-brown inclusions.

Solution in hot water: opaque, from bright-yellow to bright-brown, with non-dissolving white inclusions and characteristic honey and lemon flavor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term relief of the symptoms of cold & influenza, such as:

- increased body temperature
- nasal and sinus congestion
- minor aches and pains, such as sore throat, headache, muscle ache and sinus pain

4.2 Posology and method of administration

Posology

Adults (including the elderly) and children aged 12 years and over:

One sachet to be taken every four to six hours as required.

Maximum daily dose 5 sachets in any 24hour period.

Minimum dosing interval: 4 hours.

Not recommended for children under the age of 12 years.

Maximum duration of use without medical advice: 7 days.

Do not exceed the stated dose.

The lowest effective dose and shortest duration of treatment should be considered.

Method of administration

For oral administration only. Empty the contents of the sachet into a glass, fill with hot water, stir until dissolved. Add cold water as necessary.

4.3 Contraindications

This product is contraindicated in patients with:

- Hypersensitivity to paracetamol, phenylephrine, ascorbic acid or any of the excipients;
- Who are taking, or have taken, within the last two weeks, monoamine oxidase inhibitors, which typically are used to treat depression;
- Pheochromocytoma;
- Closed-angle glaucoma;
- Hepatic or severe renal insufficiency;
- Hypertension;
- Hyperthyroidism;
- Diabetes
- Heart disease
- Taking beta-blockers and tricyclic antidepressants.

Do not take simultaneously with other sympathomimetic decongestants.

4.4 Special Warnings and Precautions for Use

Contains paracetamol. Do not use with any other paracetamol-containing products, decongestants (medicines for the relief congestion or blocked nose) or cold and flu medicines. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol or sepsis.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were

treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

A doctor should be consulted, in these cases:

- Liver and kidney impairment
- Reduced weight or depletion
- Regular use of alcohol. You may need to avoid the use of the medicine or limit the number of received paracetamol.
- Glutathione depleted states the use of paracetamol may increase the risk of metabolic acidosis. Immediately consult the doctor if you have the following symptoms of metabolic acidosis: deep, rapid, difficult breathing; feeling sick (nausea), vomiting; loss of appetite
- Heart and vessel disease, prostatic hypertrophy (prostate problems or difficulty urinating), occlusive vascular disease (such as Raynaud's syndrome, which can appear as numbness, tingling and colour change (white, blue, then red)) in the fingers and toes when exposed to the cold)
- If you are taking the following medicines:
 - pressure control drugs (antihypertensives)
 - digoxin or similar drugs for heart diseases
 - warfarin or similar blood thinners
 - other sympathomimetics, such as decongestants, appetite suppressants, amphetamine-like psychostimulants
 - ergot alkaloids, such as ergotamine and methysergide, which are used to treat acute migraine headache
 - other medicinal products.

Contains 2468.50 mg sucrose per dose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful for people with phenylketonuria, as contains aspartame, which is the source of phenylalanine.

Contains 134.75 mg / dose of sodium. This should be taken into account in patients on a low-sodium diet.

If symptoms worsen, persist for more than 7 days or are accompanied by high body temperature, skin rash or persistent headache, contact your doctor.

Keep out of reach of children.

Always read and follow the label.

4.5 Interaction with other medicinal products and other forms of interaction

Potentially clinically significant drug interactions are listed below (see Contraindications and Warnings and Precautions).

Monoamine oxidase inhibitors (including moclobemide):	Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors.
Sympathomimetic amines	Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.
Beta-blockers, and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa)	Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased.
Tricyclic antidepressants (e.g. amitriptyline):	May increase the risk of cardiovascular side effects with phenylephrine.
Digoxin and cardiac glycosides	Concomitant use of phenylephrine may increase the risk of irregular heartbeat or heart attack.
Ergot alkaloids (e.g. ergotamine and methysergide)	Concomitant use of phenylephrine may cause increased risk of ergotism.
Warfarin and other coumarins	The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

This product should not be used during pregnancy unless the expected benefit to the mother justifies the potential risk to the fetus. This product should not be used during pregnancy without medical advice. The lowest effective dose and shortest duration of treatment should be considered.

Lactation

This product should not be used while breast feeding unless the expected benefit to the mother justifies the potential risk to the newborn. This product should not be used while breast feeding without medical advice. Phenylephrine may be excreted in breast milk.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness.

4.8 Undesirable effects

The following convention has been utilised for the classification of the frequency of adverse reactions: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Paracetamol

Adverse reactions from historical clinical trial data are both infrequent and from small patient exposure.

Adverse reactions reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are listed below by MedDRA System Organ Class.

As these reactions, have been reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown but considered likely to be very rare ($< 1/10000$):

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders	Thrombocytopaenia, agranulocytosis
Immune System disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis.
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs.
Hepatobiliary disorders	Hepatic dysfunction
Metabolic and nutrition disorders	High anion gap metabolic acidosis. Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Phenylephrine

The following adverse reactions have been observed in clinical trials with phenylephrine and may therefore represent the common adverse reactions with phenylephrine. Adverse reactions are listed below by MedDRA System Organ Class:

System Organ Class	Adverse Reaction
Psychiatric disorders	Nervousness, irritability, restlessness, and excitability
Nervous system disorders	Headache, dizziness, insomnia
Cardiac disorders	Increased blood pressure
Gastrointestinal disorders	Nausea, vomiting, diarrhoea

Adverse reactions identified during **post-marketing use** are listed below. As these reactions are reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown but considered likely to be rare or very rare.

System Organ Class	Adverse Reaction
Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma (see <i>Warnings and Precautions</i>)
Cardiac disorders	Tachycardia, palpitations
Skin and subcutaneous disorders	Hypersensitivity, allergic reactions (e.g. urticaria, allergic dermatitis, rash)
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction such as prostatic hypertrophy

While taking this drug, patients may experience: headache, dizziness, nervousness, insomnia, increased blood pressure, nausea, vomiting.

Patient should stop taking the drug and consult doctor if:

- Allergic reactions, such as skin rash or itching, sometimes with difficult breathing or swelling of lips, tongue, throat or face;
- Rash, peeling of the skin or an ulcer in the mouth;
- You have already had breathing problems when taking aspirin or other nonsteroidal anti-inflammatory drugs, as well as similar reactions when taking this drug;
- You experience unexplained bruising or bleeding;
- Heart palpitations, excessive increases in heart rate, or excessively fast irregular heartbeats;
- Blurred vision that may be associated with abnormally high blood pressure in the eyes. This reaction occurs very rarely and is more likely to occur in patients with glaucoma;
- Problem with urination. The occurrence of this reaction is more likely in patients with prostatic hyperplasia.

These reactions are rare or very rare.

4.9 Overdose

If you have taken the drug more than recommended, consult a doctor immediately because of the risk of liver failure, even if you have no symptoms.

Paracetamol

Symptoms and Signs

Paracetamol overdose may cause liver failure which can lead to liver transplant or lead to death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Treatment

Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present. Administration of N-acetylcysteine or methionine may be required.

Phenylephrine

Symptoms and Signs

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

Treatment

Treatment should be as clinically appropriate. Severe hypertension may need to be treated with an alpha blocking drug such as phentolamine.

Ascorbic Acid

Symptom and Signs

High doses of ascorbic acid (>3000mg) may cause transient osmotic diarrhoea and astrointestinal effects such as nausea and abdominal discomfort. Effects of overdose of ascorbic acid would be subsumed by serious liver toxicity caused by paracetamol overdose.

5. PHARMACOLOGICAL PROPERTIES

ATC code: N02B E51

Pharmacotherapeutic group: Other analgesics and antipyretics, paracetamol, combinations excluding psycholeptics.

5.1 Pharmacodynamic properties

Paracetamol is an analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

Paracetamol is, therefore, particularly suitable for patients with a history of disease or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).

Phenylephrine hydrochloride is a sympathomimetic agent with mainly direct effects on adrenergic receptors (predominantly alpha-adrenergic activity) producing nasal decongestion.

Ascorbic Acid (Vitamin C) is usually included in the combination of anti-cold components, compensating for the loss of vitamin C that occurs during the initial stages of viral diseases, including the common cold.

5.2 Pharmacokinetic Properties

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract and is distributed in most tissues of the body. Binding to plasma proteins is minimal at therapeutic concentrations. It is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate conjugates. Less than 5% is excreted as unmodified paracetamol.

Phenylephrine is irregularly absorbed from the gastrointestinal tract. It undergoes first-pass metabolism by monoamine oxidases in the gut and liver; orally administered phenylephrine thus has reduced bioavailability. It is excreted in the urine almost entirely as the sulphate conjugate.

Ascorbic Acid is rapidly absorbed from the gastrointestinal tract and is widely distributed throughout the body. It is 25% bound to plasma proteins. Ascorbic acid in excess of the body's needs is eliminated in the urine as metabolites.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Sodium saccharin
Sodium citrate
Lemon flavour PHS-163671
Honey flavour PFW PHS-050860
Honey flavour Felton F7624P
Caramel colour 626
Maize starch
Aspartame
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months. Should not be used after expiry date stated on a pack.

6.4 Special precautions for storage

Do not store above 25°C. Keep out of sight and reach of children.

6.5 Nature and contents of container

Powder for oral solution (honey and lemon flavour).
5 g of powder in laminate sachet (paper/polyethylene/aluminum foil/polyethylene).
10 sachets packed with patient information leaflet into a cardboard carton.

6.6 Special precautions for disposal

None

7. MANUFACTURER

SmithKline Beecham SA, Ctra. de Ajalvir, Km 2,500, Alcalá de Henares, 28806 Madrid, Spain.

8. MARKETING AUTHORIZATION HOLDER

STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany.

9. MARKETING AUTHORIZATION NUMBER**10. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION****11. DATE OF REVISION OF THE TEXT**