ALERID COLD Tablets (Cetirizine dihydrochloride + Phenylephrine hydrochloride + Paracetamol)

Composition

Each tablet contains:
Cetirizine dihydrochloride……5 mg
Phenylephrine hydrochloride……10 mg
Paracetamol……325 mg

Dosage Form

Oral tablets

Pharmacology

Pharmacodynamics

Cetirizine
Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabelled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

Phenylephrine
Phenylephrine is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly alpha adrenergic activity and is without stimulating effects on the central nervous system. The sympathomimetic effect of phenylephrine produces vasoconstriction which in turn relieves nasal congestion.

Paracetamol
Analgesic
The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

Antipyretic
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

Pharmacokinetics

Cetirizine
Absorption
Cetirizine was rapidly absorbed with a time to maximum concentration (T_{max}) of approximately 1 hour following oral administration of tablets, chewable tablets, or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. Comparable bioavailability was also found between the cetirizine tablet and the cetirizine chewable tablet, taken with or without water. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (C_{max}) of 311ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5-60 mg. Food had no effect on the extent of exposure (AUC) of the cetirizine tablet or chewable tablet, but T_{max} was delayed by 1.7 hours and 2.8 hours, respectively, and C_{max} was decreased by 23% and 37%, respectively, in the presence of food.

Distribution
The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1,000 ng/mL, which includes the therapeutic plasma levels observed.

Metabolism
A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the faeces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with the parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized, to a limited extent, by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Elimination
The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

Phenylephrine
Phenylephrine is readily absorbed after oral administration but is subject to extensive presystemic metabolism, much of which occurs in the enterocytes. As a consequence, systemic bioavailability is only about 40%. Following oral administration, peak plasma concentrations are achieved in 1-2 hours. The mean plasma half-life is in the range 2-3 hours. Penetration into the brain appears to be minimal.
Following absorption, the drug is extensively metabolised in the liver. Both phenylephrine and its metabolites are excreted in the urine.
The volume of distribution is between 200 and 500 litres, but there are no data on the extent of plasma protein binding.

Paracetamol
Paracetamol is rapidly absorbed from the gastro-intestinal tract with peak plasma concentrations occurring between 10 and 120 minutes after oral administration. It is metabolized in the liver and

excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours.

Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdose and cause liver damage.

Indications

ALERID COLD is indicated for the symptomatic treatment of allergic rhinitis, fever and nasal congestion

Dosage and Administration

Adults and children (12 years and above)

One tablet twice daily or as recommended by the physician

The recommended dosage should not be exceeded.

Contraindications

ALERID COLD is contraindicated in patients with hypersensitivity to cetirizine or its parent compound hydroxyzine.

It is also contraindicated in patients with severe hypertension or coronary artery disease, patients receiving monoamine oxidase inhibitor (MAO) therapy and in patients with hepatic dysfunction.

Contraindicated in patients with hypersensitivity to paracetamol or any of the other constituents

Warnings and Precautions

General

Cetirizine

In clinical trials, the occurrence of somnolence has been reported in some patients taking cetirizine; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of cetirizine with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Phenylephrine

This medicine should be used with caution in patients with occlusive vascular disease including Raynaud's phenomenon. Do not take for longer than 7 days, unless your doctor agrees. If symptoms do not go away talk to your doctor. Keep all medicines out of the reach of children. Warning: Do not exceed the stated dose.

Paracetamol

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Do not exceed the stated dose. Do not take with any other paracetamol-containing products. If symptoms persist for more than 3 days or get worse consult your doctor.

Drug Interactions

Cetirizine
No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400-mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.
Cetirizine hydrochloride may potentiate the effects of alcohol. Therefore caution is recommended at concomitant use of alcohol. Caution is recommended during concomitant use of CNS depressants.

Phenylephrine
Should not be given to patients being treated with monoamine oxidase inhibitors or within 14 days of stopping such treatment. May enhance the effects of anticholinergic drugs such as tricyclic antidepressants. May increase the possibility of arrhythmias in digitalised patients. May enhance the cardiovascular effects of other sympathomimetic amines (e.g. decongestants).

This medicine should not be taken together with vasodilators, Beta-blockers or enzyme inducers such as alcohol.

Paracetamol
Cholestyramine

The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone

The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Chloramphenicol: Increased plasma concentration of chloramphenicol.

Pregnancy

ALERID COLD should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

ALERID COLD is not recommended for use by lactating mothers.

Pediatric Use

ALERID COLD is not recommended for use in children below the age of 12 years.

Undesirable Effects

Cetirizine

Controlled and uncontrolled clinical trials conducted in the United States and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving cetirizine at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with cetirizine were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving cetirizine 5 or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with cetirizine was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for cetirizine were uncommon (1.0% on cetirizine vs. 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 1 lists adverse experiences in patients aged 12 years and older which were reported for cetirizine 5 and 10 mg in controlled clinical trials in the United States and that were more common with cetirizine than placebo.

Table 1. Adverse Experiences Reported in Patients Aged 12 Years and Older in Placebo-Controlled United States cetirizine Trials (Maximum Dose of 10 mg) at Rates of 2% or Greater (Percent Incidence)

Adverse Experience	Cetirizine (N=2034)	Placebo (N=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

Pediatric studies were also conducted with cetirizine. More than 1300 pediatric patients aged 6 to 11 years with more than 900 treated with cetirizine at doses of 1.25 to 10 mg per day were included in controlled and uncontrolled clinical trials conducted in the United States. The duration of treatment ranged from 2 to 12 weeks. Placebo-controlled trials up to 4 weeks duration included 168 pediatric patients aged 2 to 5 years who received cetirizine, the majority of whom received single daily doses of 5 mg. A placebo-controlled trial 18 months in duration included 399 patients aged 12 to 24 months treated with cetirizine (0.25 mg/kg bid), and another placebo-controlled trial of 7 days duration included 42 patients aged 6 to 11 months who were treated with cetirizine (0.25 mg/kg bid).

The majority of adverse reactions reported in pediatric patients aged 2 to 11 years with cetirizine were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in pediatric patients receiving up to 10 mg of cetirizine was uncommon (0.4% on cetirizine

vs. 1.0% on placebo).

Table 2 lists adverse experiences which were reported for cetirizine 5 and 10 mg in pediatric patients aged 6 to 11 years in placebo-controlled clinical trials in the United States and were more common with cetirizine than placebo. Of these, abdominal pain was considered treatment-related and somnolence appeared to be dose-related, 1.3% in placebo, 1.9% at 5 mg and 4.2% at 10 mg. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were qualitatively similar in nature and generally similar in frequency to those reported in trials with children aged 6 to 11 years.

In the placebo-controlled trials of pediatric patients 6 to 24 months of age, the incidences of adverse experiences were similar in the cetirizine and placebo treatment groups in each study. Somnolence occurred with essentially the same frequency in patients who received cetirizine and patients who received placebo. In a study of 1 week duration in children 6-11 months of age, patients who received cetirizine exhibited greater irritability/fussiness than patients on placebo. In a study of 18 months duration in patients 12 months and older, insomnia occurred more frequently in patients who received cetirizine compared to patients who received placebo (9.0% v. 5.3%). In those patients who received 5 mg or more per day of cetirizine as compared to patients who received placebo, fatigue (3.6% v. 1.3%) and malaise (3.6% v. 1.8%) occurred more frequently.

Table 2. Adverse Experiences Reported in Pediatric Patients Aged 6 to 11 Years in Placebo-Controlled United States Cetirizine Trials (5 or 10 mg Dose) Which Occurred at a Frequency of ≥2% in Either the 5 mg or the 10 mg Cetirizine Group, and More Frequently Than in the Placebo Group

		Cetirizine	
Adverse Experiences	**Placebo(N=309)**	**5 mg(N=161)**	**10 mg(N=215)**
Headache	12.3%	11.0%	14.0%
Pharyngitis	2.9%	6.2%	2.8%
Abdominal pain	1.9%	4.4%	5.6%
Coughing	3.9%	4.4%	2.8%
Somnolence	1.3%	1.9%	4.2%
Diarrhea	1.3%	3.1%	1.9%
Epistaxis	2.9%	3.7%	1.9%
Bronchospasm	1.9%	3.1%	1.9%
Nausea	1.9%	1.9%	2.8%
Vomiting	1.0%	2.5%	2.3%

The following events were observed infrequently (less than 2%), in either 3982 adults and children 12 years and older or in 659 pediatric patients aged 6 to 11 years who received cetirizine in U.S. trials, including an open adult study of six months duration. A causal relationship of these infrequent events with cetirizine administration has not been established.

Autonomic Nervous System: anorexia, flushing, increased salivation, urinary retention.

Cardiovascular: cardiac failure, hypertension, palpitation, tachycardia.

Central and Peripheral Nervous Systems: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.

Gastrointestinal: abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.

Genitourinary: cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.

Hearing and Vestibular: deafness, earache, ototoxicity, tinnitus.

Metabolic/Nutritional: dehydration, diabetes mellitus, thirst.

Musculoskeletal: arthralgia, arthritis, arthrosis, muscle weakness, myalgia.

Psychiatric: abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.

Respiratory System: bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.

Reticuloendothelial: lymphadenopathy.

Skin: acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.

Special Senses: parosmia, taste loss, taste perversion.

Vision: blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.

Body as a Whole: accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine has been reported.

Post marketing Experience

In the post marketing period, the following additional rare, but potentially severe adverse events have been reported: aggressive reaction, anaphylaxis, cholestasis, convulsions, glomerulonephritis, hallucinations, haemolytic anaemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, suicidal ideation, suicide, and thrombocytopenia.

Phenylephrine
Adverse effects may include tachycardia, cardiac arrhythmias, palpitations, hypertension, nausea, vomiting, headache and occasionally urinary retention in males.

Paracetamol
Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causality related to paracetamol.

Overdosage

Cetirizine

Overdosage has been reported with cetirizine. In one case, an adult patient who took 150 mg of cetirizine was somnolent, but did not display any other clinical signs or abnormal blood chemistry or haematology results. In an 18-month old paediatric patient who took an overdose of cetirizine (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness.

Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless a dialysable agent has been concomitantly ingested.

Phenylephrine

Symptoms of overdosage include irritability, restlessness, palpitations, hypertension, difficulty in micturition, nausea, vomiting, thirst and convulsions. In severe overdosage gastric lavage and aspiration should be performed. Symptomatic and supportive measures should be undertaken, particularly with regard to cardiovascular and respiratory systems. Convulsions should be controlled with intravenous diazepam. Chlorpromazine may be used to control marked excitement and hallucinations. Severe hypertension may need to be treated with an alpha-adrenoreceptor blocking drug, such as phentolamine. A beta blocker may be required to control cardiac arrhythmias.

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors

If the patient

OR

1. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
2. Regularly consumes ethanol in excess of recommended amounts.
3. Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic

failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however, the maximum protective effect is obtained up to 8 hours "Post Ingestion".

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

Packaging Information

ALERID COLD Tablets: Strip of 10 tablets

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