1. NAME OF THE MEDICINAL PRODUCT

Alben Cold Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains:
Paracetamol B.P 100mg
Chlorpheniramine Maleate.....1mg
Pseudoephedrine HCl.....9.38mg

Excipients with known effect:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- Oral Drops
- A Pink Liquid

4. Clinical Particulars

4.1 Therapeutic indications

Alben cold is indicated in the relief of aches associated with common cold, headache, and for the relief of fever.

4.2 Posology and method of administration

- Posology
  Up to 3months old: 0.4ml every 4-6 hours.
  4-11months: 1ml(1 dropperful) every 4-6 hours.
  Or as prescribed by the physician. If symptoms persist after 2days, consult your doctor.

- Method of administration

For oral administration only.

4.3 Contraindications

- Hypersensitivity to paracetamol, chlorpheniramine maleate, pseudoephedrine HCl or to any of the excipients listed in section 6.1.
- Patients with severe hepatic dysfunction.
- Patients who are currently taking other sympathomimetic decongestants.
- Patients who have been treated with MAOIs within the last fourteen days.

4.4 Special warnings and precaution for use

This product should not be given to premature infants. Caution should also be observed in patients with severe cardiovascular disorder. Care is advised in the administration of this product to patients with severe

renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Chronic alcohol users should consult a doctor before use.

4.5 Interactions with other medicinal products and other forms of interaction

The hepatotoxicity of Paracetamol, particularly after overdosage, may be increased by drugs which induce liver microsomal enzymes such as carbamazepine, barbiturates (e.g. phenobarbital), fosphenytoin, phenytoin, primidone, tricyclic antidepressants, and alcohol.

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

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.

Concurrent use of chlorphenamine and hypnotics or anxiolytics may cause an increase in sedative effects, concurrent use of alcohol may have a similar effect therefore medical advice should be sought before taking chlorphenamine concurrently with these medicines.
Chlorphenamine inhibits phenytoin metabolism and can lead to phenytoin toxicity.
The anticholinergic effects of chlorphenamine are intensified by MAOIs (see Contra-indications).

Sympathomimetic agents: Concomitant use of this medicine with tricyclic antidepressants, or with other sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants), may cause a rise in blood pressure.

This medicine should not be given to patients treated with MAOIs or within 14 days of stopping treatment as there is an increased risk of hypertensive crisis.

4.6 Pregnancy and Lactation

Pregnancy

Not to be used during pregnancy unless considered essential by a physician.

Breast-feeding

Not to be used during pregnancy unless considered essential by a physician.

4.7 Effects on ability to drive and use machines

This product may have a minor influence on the ability to drive and use machines. This product may cause drowsiness, dizziness, blurred vision and psychomotor impairment. Patients should be cautioned about engaging in activities such as driving a car or operating machinery, until they have established their own response to the drug.

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post marketing experience with paracetamol are listed below by System Organ Class (SOC)

The frequencies are defined according to the following convention:

Very common ≥1/10

Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from available data).

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.

System Organ Class (SOC)	**Frequency**	**Adverse Drug Reaction (Preferred Term)**
Blood and lymphatic system disorders	Not known	Blood disorder (including thrombocytopenia and agranulocytosis) [1]
Immune System Disorders	Very rare Very rare	Anaphylactic reaction Hypersensitivity
Hepatobiliary disorders	Not known	Liver injury[2]
Skin and Subcutaneous Tissue disorders	Very rare	Rash
	Not known	Fixed eruption
	Not known	Rash pruritic
	Not known	Urticaria
Renal and urinary disorders	Uncommon	Nephropathy toxic
	Not known	Renal papillary necrosis[3]
Investigations	Not known	Transaminases increased[4]
Vascular Disorders	Not known	Hypertension
Gastrointestinal Disorders	Not known	Ischaemic colitis Vomiting
Nervous System Disorders	Sedation, somnolence	Very common
	Disturbance in attention, abnormal coordination, dizziness headache	Common

4.9 Overdose

Paracetamol

Liver damage is possible in adults and adolescents (≥12 years of age) who have taken 7.5g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. 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

a) Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b) Regularly consumes ethanol in excess of recommended amounts

Or

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, hyperhidrosis, malaise, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis.

Abnormalities of glucose metabolism and metabolic acidosis may occur. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased.

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.

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

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. The effectiveness of the antidote declines sharply after this time. 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 24h from ingestion should be discussed with the NPIS or a liver unit.

<u>Chlorpheniramine maleate</u>

Symptoms and signs
The estimated lethal dose of chlorphenamine is 25 to 50mg/kg body weight. Symptoms and signs include sedation, paradoxical excitation of the CNS, toxic psychosis, convulsions, apnoea, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias.
Treatment
Management should be as clinically indicated or as recommended by the national poisons centres where available. Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. If overdosage is by the oral route, treatment with activated charcoal should be considered provided there are no contraindications for use and the overdose has been taken recently (treatment is most effective if given within an hour of ingestion). Treat hypotension and arrhythmias vigorously. CNS convulsions may be treated with i.v. diazepam. Haemoperfusion may be used in severe cases.

<u>Pseudoephedrine HCl</u>

Signs and symptoms: Overdosage may result in: Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia Psychiatric disorders: CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses Nervous system disorders: seizures, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children Eye disorders: mydriasis Cardiac disorders: palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction Vascular disorders: hypertension, hypertensive crisis Gastrointestinal disorders: nausea, vomiting, ischaemic bowel infarction Musculoskeletal and connective tissue disorders:

rhabdomyolysis Renal and urinary disorders: acute renal failure, difficulty in micturition Management: Necessary measures should be taken to maintain and support respiration and control convulsions. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.

5. Pharmacological properties:

5.1 Pharmacodynamic properties

Paracetamol

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 sensitise pain receptors to mechanical or chemical stimulation.

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

Chlorpheniramine maleate

Chlorphenamine is a potent antihistamine (H_1-antagonist).
Antihistamines diminish or abolish the actions of histamine in the body by competative reversible blockade of histamine H_1-receptor sites on tissues. Chlorphenamine also has anticholinergic activity.
Antihistamines act to prevent the release of histamine, prostaglandins and leukotrines and have been shown to prevent the migration of inflammatory mediators. The actions of chlorphenmine include inhibition of histamine on smooth muscle, cappillary permeability and hence reduction of oedema and wheal in hypersensitivity reactions such as allergy and anaphylaxis.

Pseudoephedrine HCl

Pseudoephedrine has direct and indirect sympathomimetic activity and is an orally effective upper respiratory tract decongestant. Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and considerably less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes which lasts for at least 4 hours

5.2 Pharmacokinetic properties

Paracetamol

Oral absorption is rapid and almost complete, it may be decreased if Paracetamol is taken following a high carbohydrate meal.

There is no significant protein binding with doses producing plasma concentrations of below 60mcg (µg)/ml, but may reach moderate levels with high or toxic doses.

Approximately 90 - 95% of a dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite, which may accumulate in overdosage after primary metabolic pathways become saturated, is hepatotoxic and possibly nephrotoxic.

Half life is 1 to 4 hours; does not change with renal failure but may be prolonged in acute overdosage, in some forms of hepatic disease, in the elderly, and in the neonate; may be somewhat shortened in children.

Time to peak concentration, 0.5 - 2 hours; peak plasma concentrations, 5 - 20mcg (µg)/ml (with doses up to 650mg); time to peak effect, 1- 3 hours; duration of action, 3- 4 hours.

Elimination is by the renal route, as metabolites, primarily conjugates, 3% of a dose may be excreted unchanged.

Peak concentration of 10 - 15mcg(µg)/ml have been measured in breast milk, 1 - 2 hours following maternal ingestion of a single 650mg dose. Half life in breast milk is 1.35 - 3.5 hours.

Chlorpheniramine maleate

Chlorphenamine is well absorbed from the gastro-intestinal tract, following oral administration. The effects develop within 30 minutes, are maximal within I to 2 hours and last 4 to 6 hours. The plasma half-life has been estimated to be 12 to 15 hours.
Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivatives. About 22% of an oral dose is excreted unchanged in the urine.

Pseudoephedrine HCl

In healthy adult volunteers, the administration of 60 mg psuedoephedrine resulted in a peak plasma concentration (Cmax) of approximately 180 ng/ml occurring at about 2 hours (Tmax) post dose. The plasma half-life was approximately 5.5 hours (urine pH maintained between 5.0-7.0). The plasma half-life of pseudoephedrine is markedly decreased by acidification of the urine and increased by alkalinization. Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Excretion is mainly via the urine, 55% to 75% of a dose is excreted unchanged.

5.3 Preclinical safety data

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

6. Pharmaceutical particulars

6.1 List of excipients

- HydroxyEthylMethylCellulose
- Propylene Glycol
- Strawberry Flavour
- Ethanol
- Methyl paraben
- Carmoisine Red
- Menthol
- Purified Water

6.2 Incompactibilities

- Not Applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

- Store in a cool dry place below 30°C protected from light and out of reach of children.

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

Each cardboard box contains one bottle of 20ml PET bottle with metallic screw cap and a dropper.

Pack size: 15ml

6.6 Special precautions for disposal<and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Applicant/Manufacturer

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