National Agency for Food & Drug Administration & Control

(NAFDAC)

Registration & Regulatory Affairs (R & R)

Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT
Avrobabe Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml of Avrobabe Syrup contains Paracetamol 120mg, Chlorpheniramine Maleate 0.50mg and Concentrated Dill Water 0.10ml

3. PHARMACEUTICAL FORM
Syrup
Colourless syrup

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Avrobabe Syrup is indicated for the relief of mild to moderate pain and as an antipyretic. It can be used in many conditions including headache, toothache, earache, teething, sore throat, colds & influenza, aches and pains and post-immunisation fever. Avrobabe syrup is also indicated for the symptomatic control of all allergic conditions responsive to antihistamines, including hay fever, vasomotor rhinitis, urticaria, angioneurotic oedema, food allergy, drug and serum reactions, insect bites and pruritus (itching).

4.2 Posology and method of administration
Oral administration only
Do not exceed the stated dose or frequency of dosing

Infants aged 3 months - 1 year: 2.5ml – 5ml.
Children aged 2 - 6 years: 5ml – 10ml.
Children over 6 years: 10ml – 20ml
Dosage may be given up to four times daily.
Do not exceed the stated dose.
Do not give more than 4 doses in any 24 hour period.
If symptoms persist after 4 days, consult your doctor.

4.3 Contraindications
Hypersensitivity to paracetamol, antihistamines or to any of the syrup ingredients.
Avrobabe Syrup is contra-indicated in patients with severe hepatic dysfunction.
The anticholinergic properties of chlorphenamine are intensified by monoamine oxidase inhibitors (MAOIs). Avrobabe Syrup is therefore contra-indicated in patients who have been treated with MAOIs within the last fourteen days.

4.4 Special warnings and precautions for use
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.
Chlorphenamine, in common with other drugs having anticholinergic effects, should be used with caution in epilepsy; raised intra-ocular pressure including glaucoma; prostatic hypertrophy; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis or asthma; hepatic impairment; renal impairment.
Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (eg. Increased energy, restlessness, nervousness).
The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.
The effects of alcohol may be increased and therefore concurrent use should be avoided.
Should not be used with other antihistamine containing products, including antihistamine containing cough and cold medicines.
Avrobabe contains paracetamol. Do not give with other products containing paracetamol.

Keep out of the reach and sight of children.

4.5 Interaction 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 barbiturates, tricyclic antidepressants, and alcohol.

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.
Regular use of Paracetamol possibly reduces metabolism of Zidovudine (increased risk of neutropenia).
The use of drugs that induce hepatic microsomal enzymes such as anticonvulsants and oral contraceptives may increase the extent of metabolism of paracetamol resulting in reduced plasma concentrations of the drug and a faster elimination rate.

Concurrent use of chlorphenamine and hypnotics or anxiolytics may cause an increase in sedative effects, 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).

4.6 Pregnancy and lactation
Pregnancy
There are no adequate data from the use of chlorphenamine in pregnant women. The potential risk for humans is unknown, Use during the third trimester may result in reactions in the newborn or premature neonates. Not to be used during pregnancy unless considered essential by a physician.

Lactation
Chlorphenamine maleate and other antihistamines may inhibit lactation and may be secreted in breast milk. Not to be used during lactation unless considered essential by a physician.

4.7 Effects on ability to drive and use machines
The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment, which can seriously hamper the patients' ability to drive and use machinery.

4.8 Undesirable effects
Side effects are rare and usually mild. The most reported being gastrointestinal disturbances like nausea, vomiting, epigastric pain, loss of appetite, constipation or diarrhoea and their incidence might be reduced by giving the drug with meals. Headache, Hypersensitivity reactions and rashes may also occur.
Other reported side effects are sedation and CNS depression including dizziness, lassitude, blurred vision and incordination, which may diminish after few days of treatment. Concurrent ingestion of alcohol or other CNS depressants produce an additive effect that impairs motor skills.
Less commonly reported are psychomotor impairment, antimuscarinic effects like dry mouth, thickened respiratory tract secretions, urinary retention or frequency, dysuria and increased gastric reflux.

*Children and the elderly are more susceptible to neurological anticholinergic effects and paradoxical excitation (eg increased energy, restlessness, nervousness)

4.9 Overdose
Symptoms and signs
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, phenobarbitone, 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 deplete e.g, eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

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.

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

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 the 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 concentrations 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 patient who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. Treat hypotension and arrhythmias vigorously. CNS convulsions may be treated with i.v. diazepam. Haemoperfusion may be used in severe cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol

ATC Code: N02 BE01

Paracetamol has analgesic and antipyretic effects that do not differ significantly from those of aspirin. However it has only weak anti-inflammatory effects. It is only a weak inhibitor of prostaglandin biosynthesis although there is some evidence to suggest it may be more effective against enzymes in the central nervous system than in the periphery. This may in part account for its activity profile.

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.

Chlorphenamine

ATC Code R06AB02
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 oedma and wheal in hypersneitivity reactions such as allergy and anaphylaxis.

Concentrated Dill Water

Concentrated Dill water is prepared from Dill oil which is a carminative. It is also a flavour.

5.2 Pharmacokinetic properties

Paracetamol

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring 0.5-2 hours after dosing. The plasma half-life is approximately 2 hours after therapeutic doses in adults but is increased in neonates to about 5 hours.
Distribution
It is widely distributed through the body.
Biotransformation
Metabolism is principally by the hepatic microsomal enzymes and urinary excretion accounts for over 90% of the dose within 1 day. Virtually no paracetamol is excreted unchanged, the bulk being conjugated with glucoronic acid (60%), sulphuric acid (35%) or cysteine (3%).
Children have less capacity for glucuronidation of the drug than adults.
Elimination
Following therapeutic doses 90-100% of the drug is recovered in the urine within 24 hours.

Chlorphenamine

Chlorphenamine is well absorbed from the gastro-intestinal tract, following oral administration. The effects develop within 30 minutes, are maximal within 1 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.

5.3 Preclinical safety data

No additional data of relevance.

6. Pharmaceutical particulars

6.1 List of excipients

Conc. Dill Water
Propylene Glycol
Sucrose
Sorbitol Solution
Sodium Benzoate

6.2 Incompatibilities
None known

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30°C. Protect from light

6.5 Nature and contents of container
Amber PET bottle containing 60ml Avrobabe Syrup. Supplied with a plastic measuring cup

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

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