1. NAME OF THE MEDICINAL PRODUCT

Avro Chesty Cough Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml syrup contains:-

Bromhexine hydrochloride 8mg
Guaifenesin 100mg
Pseudoephedrine hydrochloride 60mg

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Syrup for oral administration
A red-coloured, clear, slightly viscous oral liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Avro Chesty Cough Syrup

- Chesty Coughs
- Nasal and chest congestions
- Blocked Nose
- Catarrh and runny nose

Avro Chesty Cough Syrup reduces congestion in the upper respiratory tract, including the nose, nasal passages and sinuses, making it easier to breathe. It also relieves chest congestion from accumulation of mucus in the respiratory air passages by loosening and thinning thick mucus associated with chesty coughs and making it easier to cough up.

Avro Chesty Cough Syrup relieves stuffy and blocked nose and sinuses, making it easier to breathe.

4.2 Posology and method ofadministration

Posology
Adults & Children over 12 years: 10 mL
Children 6 - 12 years: 5 mL
Children 2 - 5 years: 2.5 mL

Accurately measure the dose with a medicine measure provided.

May be taken every 4 - 6 hours as required with a maximum of 4 doses in 24 hours.
Do not take more than 4 doses in 24 hours. If symptoms persist, seek medical attention

The elderly
Normal adult dosage is appropriate.

Hepatic dysfunction
Experience with the use of the product suggests normal adult dosage is appropriate, although it may be prudent to exercise caution in the presence of severe hepatic impairment.

Renal dysfunction
Caution should be exercised when administering this product to patients with moderate to severe renal impairment, particularly if accompanied by cardiovascular disease.
Method of administration:
For oral administration only.

4.3 Contraindications

- Avro Chesty Cough Syrup is contraindicated in individuals who have previously exhibited intolerance to pseudoephedrine Bromhexine or Guaifenesin.
- Avro Chesty Cough Syrup is contraindicated in patients with cardiovascular disease including severe hypertension or severe coronary artery disease and individuals taking beta blockers (see section 4.5).
- This product is contraindicated in individuals who are concomitantly taking other sympathomimetic decongestants.
- This product is contraindicated in individuals with diabetes mellitus, closed angle glaucoma, hyperthyroidism, phaeochromocytoma or severe renal impairment.
- This product is contraindicated in individuals who are taking, or have taken, monoamine oxidase inhibitors within the preceding 14 days. The concomitant use of pseudoephedrine and this type of product may cause a rise in blood pressure and/or hypertensive crisis.
- The antibacterial agent furazolidone, is known to cause a dose-related inhibition of monoamine oxidase. Although there are no reports of hypertensive crises caused by the concurrent administration of Pseudoephedrine and furazolidone they should not be taken together.
- Avro Chesty Cough Syrup should not be taken during pregnancy or when planning to become pregnant.

4.4 Special warnings and precautions for use

Before you start to take Avro Chesty Cough Syrup, tell your physician if you have allergies to any other medicines or foods.

Consult a physician before using this product if you have or have had any of the following medical conditions:

- high blood pressure
- overactive thyroid gland
- diabetes
- heart disease and poor blood flow in the blood vessels of the heart
- glaucoma (high pressure in the eyes)
- difficulty in urination and/or enlargement of the prostate
- liver or kidney disease
- stomach ulcers
- asthma
- chronic bronchitis or acute or chronic bronchial asthma
- chronic obstructive pulmonary disease (COPD)
- emphysema
- smoker's cough
- porphyria, a rare blood pigment disorder

Ask your physician about taking this medicine if you are breastfeeding.

Patients with thyroid disease who are receiving thyroid hormones should not take pseudoephedrine unless directed by a physician.

Do not take with a cough suppressant.

This product should be not used for persistent or chronic cough, such as occurs with asthma, or emphysema where cough is accompanied by excessive secretions, unless directed by a physician. Patients should be advised to consult a physician if their cough lasts for more than 5 days or comes back, or is accompanied by a fever, rash or persistent headache.
Caution should be exercised when using the product in the presence of severe hepatic impairment or moderate to severe renal impairment (particularly if accompanied by cardiovascular disease), [See section 5.2], or occlusive vascular disease.
If any of the following occur, this medicine should be stopped
Hallucinations
Restlessness
Sleep disturbances

Severe Skin reactions
Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of this drug should be discontinued and appropriate measures taken if needed.

Ischaemic colitis
Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy
Cases of ischaemic optic neuropathy have been reported with pseudoephedrine.
Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

If symptoms do not go away talk to your doctor.

4.5 Interaction with other medicinal products and other forms of interaction

Pseudoephedrine

MAOIs and/or RIMAs: Pseudoephedrine exerts its vasoconstricting properties by stimulating α-adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since MAOIs impede the metabolism of sympathomimetic amines and increase the store of releasable norepinephrine in adrenergic nerve endings, MAOIs may potentiate the pressor effect of pseudoephedrine. This medicine should not be used in patients treated with MAOIs or within 14 days of stopping treatment as there is an increased risk of hypertensive crisis.

Sympatomimetic agents: Concomitant use of Sinucof with sympathomimetic agents, such as decongestants, tricyclic antidepressants, appetite suppressants and amphetamine-like psychostimulants may cause a rise in blood pressure

Antihypertensives: Because of its pseudoephedrine content, Sinucof may partially reverse the hypotensive action of drugs which interfere with sympathetic activity including bretylium, betanidine, guanethidine, debrisoquine, methyldopa, adrenergic neurone blockers, alpha-and beta-adrenergic blocking agents.

Moclobemide: Risk of hypertensive crisis.

Cardiac glycosides: increased risk of dysrythmias.

Ergot alkaloids (ergotamine & methysergide): increased risk of ergotism.

Oxytocin: risk of hypertension.

Anaesthetic agents: Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

Bromhexine
Inform your doctor or pharmacist if you are taking any antibiotics as bromhexine may increase the absorption of antibiotics.

Guaifenesin
If urine is collected within 24 hours of a dose of guaifenesin a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

4.6 Pregnancy and Lactation

This product should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus or breastfeeding infant.

Pregnancy
There are limited amount of data on the use of Bromhexine, Pseudoephedrine, Guaifenesin or the combination of all 3 actives in pregnant women. Although, the use of pseudoephedrine during the first trimester of pregnancy has been associated with an increased frequency of gastroschisis (a developmental defect in the abdominal wall with intestinal herniation) and of small intestinal atresia (congenital obstruction of small intestine). Due to the vasoconstrictive properties of pseudoephedrine, it may induce a reduction in uteroplacental circulation. Pseudoephedrine is not recommended in pregnancy.

The safety of bromhexine in pregnant women is unknown. Therefore, it is given to pregnant women only if the doctor thinks the benefits outweigh the risks.

Breastfeeding
Pseudoephedrine has been detected in human milk with a small percentage of the maternal dose potentially administered to the breastfed infant. It has been estimated that approximately 0.5 to 0.7% of a single dose of pseudoephedrine ingested by a mother will be excreted in the breast-milk over 24 hours. Irritability and disturbed sleep have been reported in breastfed infants. Pseudoephedrine may suppress lactation.

The amounts of guaifenesin secreted into breast milk are considered too small to be harmful.
It is unknown whether bromhexine is excreted in human milk. Bromhexine is given to breastfeeding mothers only if the doctor thinks benefits are more significant than risks.

4.7 Effects on ability to drive and use machines
No or negligible influence.

4.8 Undesirable effects

Guaifenesin
The following side effects may be associated with the use of guaifenesin:
Gastrointestinal disorders: Nausea, vomiting, gastrointestinal discomfort.
Immune system disorders: Hypersensitivity reactions.

Pseudoephedrine
Cardiovascular disorders: Tachycardia, palpitations, other cardiac dysrhythmias.
Eye disorders: Frequency unknown - Ischaemic optic neuropathy
Gastrointestinal disorders: Nausea and/or vomiting.
Frequency unknown: Ischaemic colitis

General disorders and administration site conditions: Irritability.
Immune system disorders: Hypersensitivity reactions, including cross-sensitivity that may occur with other sympathomimetics.
Nervous system disorders: Headache, tremor, anxiety, restlessness, excitability, dizziness, insomnia, hallucinations (particularly in children) and paranoid delusions.
Psychiatric disorders: Confusion and sleep disturbance.
Renal and urinary disorders: Difficulty in micturition including urinary retention.
Skin and subcutaneous tissue disorders: Skin reactions including rash.
Frequency unknown - Severe skin reactions, including acute generalized exanthematous pustulosis (AGEP).
Vascular disorders: Hypertension.

Tell your physician if you notice any of the following and they worry you:

- drowsiness
- difficulty sleeping
- nervousness
- excitability
- restlessness
- dizziness
- fear or anxiety
- rapid heart beat
- tremor
- hallucinations
- nausea
- diarrhoea
- indigestion
- abdominal fullness
- headache
- sweating

The above list includes the more common side effects of this medicine. They are usually mild and short-lived. Children and people over 65 years of age may have an increased chance of getting side effects.

If symptoms persist or worsen consult your physician.

4.9 Overdose

Symptoms of overdosage include irritability, restlessness, palpitations, hypertension, difficulty in micturition, nausea, vomiting, thirst and convulsions. When taken in excess, guaifenesin may cause renal calculi.
Overdose in pseudoephedrine may result in: Hyperglycaemia, hypokalaemia, CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses, seizures, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children, mydriasis, palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction, hypertension, vomiting, ischaemic bowel infarction, acute renal failure, difficulty in micturition

Management
In severe overdosage gastric lavage and aspiration should be performed. Symptomatic and supportive measures should be undertaken particularly with regard to the 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

General properties

ATC Code: R05CA03; Pharmacotherapeutic Group: Cough and Cold Preparations, Expectorants.

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 of systolic blood pressure and considerably less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes, persisting for at least 4 hours.
Pseudoephedrine and its salts are given by mouth for the symptomatic relief of nasal congestion. Pseudoephedrine is usually combined with other ingredients for the relief of cough and cold symptoms.

Guaifenesin is an expectorant that loosens and reduces the thickness of phlegm, making it easier to cough up. Guaifenesin is reported to increase the volume and reduce the viscosity of tenacious sputum and is used as an expectorant for productive cough. It is usually given in oral doses of 200 to 400mg every 4 hours.
It is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain which in mm enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.
An FDA review of preparations available over-the-counter concluded that guaifenesin was an effective expectorant. A study found that guaifenesin also appeared to reduce cough reflex sensitivity in patients with upper respiratory tract infections, which produce a transient increase in sensitivity, although it had no effect on cough reflex in healthy subjects. The mechanism for this effect was unclear.

Bromhexine is a mucloytic used in the treatment of respiratory disorders associated with productive cough. It works by altering the structure of mucus to decrease its viscosity; thereby facilitating its removal by ciliary action or expectoration.

5.2 Pharmacokinetic properties

Absorption
Pseudoephedrine is readily and completely absorbed from the gastrointestinal tract. It is resistant to metabolism by monoamine oxidase and is largely excreted in the urine unchanged. It has an elimination half-life of 5 to 8 hours but its urinary elimination and hence half-life is pH dependent. Pseudoephedrine is rapidly distributed throughout the body, its volume of distribution being 2 to 3L/kg bodyweight.

Guaifenesin is readily absorbed from the gastrointestinal tract. It is rapidly metabolised and excreted in the urine.

Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract,; peak plasma concentrations occur after about 1hour. Bromhexine undergoes extensive first-pass metabolism in the liver: its oral bioavailability is stated to be only about 20%.It is widely distributed to body tissues. About 85 to 90% of a dose is excreted in the urine mainly as metabolites.

Bromhexine is highly bound to plasma proteins. It has a terminal elimination half-life of 13-40hours.It crosses the blood-brain barrier and small amounts cross the placenta.

Distribution
The apparent volume of distribution of pseudoephedrine (Vd/F) was approximately 2.8 l/kg.

No information is available on the distribution of guaifenesin in humans.

Bromhexine is widely distributed to body tissues.

Metabolism and Elimination
The t½ for pseudoephedrine was approximately 5.5 hours. Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine; 55 % to 90 % of a dose is excreted unchanged. The apparent total body clearance of pseudoephedrine (Cl/F) was approximately 6 - 6.5 ml/min/kg. The rate of urinary elimination is accelerated when the urine is acidified. Conversely, as the urine pH increases, the rate of urinary elimination is slowed.

Guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaifenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours. It is excreted in the urine.

Bromhexine undergoes extensive first-pass metabolism in the liver: its oral bioavailability is stated to be only about 20%. About 85 to 90% of a dose is excreted in the urine mainly as metabolites.

Pharmacokinetics in the Elderly

After the administration of a pseudoephedrine-containing product (8 mg acrivastine + 60 mg pseudoephedrine) to elderly volunteers, the t½ for pseudoephedrine was 1.4 fold that seen in younger healthy volunteers. The apparent Cl/F was 0.8 fold that seen in younger healthy volunteers, and the Vd/F was essentially unchanged.

There have been no specific studies of this product, pseudoephedrine or guaifenesin in the elderly.

5.3 Preclinical safety data
The results of pre-clinical studies do not add anything of relevance for therapeutic purpose as the active ingredients of this product are well known constituents of medicinal products.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Propylene Glycol
SCMC
Amaranth
Caramel
Glycerol
Sorbitol Solution
Acesulfame Potassium
Citric Acid Monohydrate
Sodium Benzoate
Methyl Hydroxybenzoate
Propyl Hydroxybenzoate
Raspberry Flavour
Menthol
Deionised Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container

100 ml bottles with Ropp cap.

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

APPLICANT

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