For the use only of a Registered Medical Practitioners

℞ Terbutaline Sulphate, Guaiphenesin, Bromhexine Hydrochloride & Menthol Syrup

ALKOF®+

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1. NAME OF THE MEDICINAL PRODUCT

Terbutaline Sulphate, Guaiphenesin, Bromhexine Hydrochloride & Menthol Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:

Terbutaline Sulphate IP	1.25 mg
Guaiphenesin IP	50 mg
Bromhexine Hydrochloride IP	2 mg
Menthol IP	0.5 mg
Flavoured Syrupy base	q.s.

3. PHARMACEUTICAL FORM

Syrup for oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Terbutaline sulphate, Bromhexine Hydrochloride and Guaiphenesin expectorant is indicated for clinical relief of productive cough associated with bronchitis, bronchial asthma, emphysema and other bronchopulmonary disorders where bronchospasm, mucous plugging and problems of expectoration co-exist.

4.2 Posology and Method of Administration

Adults:

10-20 ml thrice-daily Children (6-12 years): 5-10 ml thrice daily

4.3 Contraindications

Hypersensitivity to any of the components of the formulation. It should not be used in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.

It is also contraindicated in patients with gastric ulceration. Not recommended for children under 6 years of age.

4.4 Special Warnings and Special Precautions for Use

Terbutaline:

As for all beta2-agonists caution should be observed in patients with thyrotoxicosis.

Cardiovascular effects may be seen with sympathomimetic drugs, including terbutaline. There is some evidence from post-marketing data and published literature of myocardial ischaemia associated with beta agonists.

Due to the positive inotropic effect of beta2-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy.

Tocolysis:

Terbutaline should be used with caution in tocolysis and supervision of cardiorespiratory function, including ECG monitoring, should be considered. Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Terbutaline should not be used as a tocolytic agent in patients with significant risk factors for or pre-existing heart disease.

During infusion treatment in pregnant women with beta2-stimulants in combination with corticosteroids a rare complication with a pathological picture resembling pulmonary oedema, has been reported.

Increased tendency to uterine bleeding has been reported in connection with Caesarean section. However, this can be effectively stopped by propranolol 1-2 mg injected intravenously.

Respiratory indications:

Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving Terbutaline should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease.

Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Due to the hyperglycaemic effects of beta2-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments. It is recommended that serum potassium levels are monitored in such situations.

If a previously effective dosage regimen no longer gives the same symptomatic relief, the patient should urgently seek further medical advice. Consideration should be given to the requirements for additional therapy (including increased dosages of anti-inflammatory medication). Severe exacerbations of asthma should be treated as an emergency in the usual manner.

Bromhexine:

Patients being treated with bromhexine should be notified of an expected increase in the flow of secretions.

The use of Bromhexine without medical supervision is not intended in patients who suffer from such condition chronically.

Medical advice should be sought if the symptoms last longer than 14 days and/or if the symptoms increase in spite of treatment with bromhexine.

Since mucolytics may disrupt the gastric mucosal barrier bromhexine should be used with care in patients with a history of peptic ulcer disease (gastric ulcer).

Care is also advisable in asthmatic patients.

Clearance of bromhexine or its metabolites may be reduced in patients with severe hepatic or renal impairment.

Bromhexine may increase the amount of antibiotic penetration. Antibiotics are medicines used to treat infections.

Guaiphenesin:

Guaiphenesin should be not used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a physician should be consulted. Caution should be exercised in the presence of severe renal or severe hepatic impairment. The concomitant use of cough suppressants is not recommended. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Not more than 4 doses should be given in any 24 hours. Avoid with any other cough and cold medicine. Consult a pharmacist or other healthcare professional before use in children under 6 years.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction Terbutaline:

Beta-blocking agents (including eye drops); especially the non-selective ones such as propranolol, may partially or totally inhibit the effect of beta-stimulants. Therefore terbutaline preparations and non-selective beta-blockers should not normally be administered concurrently. Terbutaline should be used with caution in patients receiving other sympathomimetic.

Hypokalaemia may result from beta2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics.

Bromhexine:

Bromhexine may increase the concentration of concurrently administered antibiotics in bronchial secretions. No clinically relevant interactions with other medications have been reported.

Guaiphenesin:

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

Others

Terbutaline sulphate, Bromhexine Hydrochloride and Guaiphenesin Expectorant should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.

4.6 Fertility, Pregnancy and Lactation

Pregnancy However, there are no adequate and well-controlled studies of this combination in pregnant women. Hence this combination should be administered with caution in pregnancy.

Lactation It is not known whether this combination is secreted in breast milk. However terbutaline is secreted in breast milk, but effect onthe infant is unlikely at therapeutic doses. Therefore this combination should be used with caution nursing mothers.

4.7 Effects on Ability to Drive and Use Machines

Most common adverse reactions to terbutaline are tremor, headache, tachycardia, palpitations, muscle spasms and hypokalaemia, this may affects ability to drive and useof machines.

4.8 Undesirable Effects Terbutaline

Most of the adverse reactions are characteristic of sympathomimetic amines. The majority of these effects have reversed spontaneously within the first 1-2 weeks of treatment. The frequency of side-effects is low at the recommended doses.

The most common adverse reactions to terbutaline are tremor, headache, tachycardia, palpitations, muscle spasms and hypokalaemia.

Rare cases of arrhythmias e.g. atrial fibrillation, supraventricular tachycardia and extra systoles, myocardial ischaemia, peripheral vasodilation, hypersensitivity reactions including angioedema, bronchospasm, hypotension, collapse, nausea, mouth and throat irritation, sleep disorder, behavioural disturbances such as agitation and restlessness, paradoxical bronchospasm, urticaria and rash.

Bromhexine

Dermatologic Effects: skin rash, urticaria,

Gastrointestinal Effects: nausea, epigastric pain, vomiting, and diarrhoea Hepatic Effects: Transient elevations in serum aminotransferase levels Neurologic Effects (Central nervous system): dizziness and headache Renal Effects: Nocturnal enuresis

Others:

- anaphylaxis
- bronchospasm,; difficulty in breathing
- angioedema; swelling of the face, lips, mouth, tongue or throat which maycause difficulty swallowing or breathing.

Guaiphenesin

Side effects resulting from guaifenesin administration are very rare. Guaiphenesin has occasionally been reported to cause gastro-intestinal discomfort, nausea and vomiting, particularly in very high doses. Also, hypersensitivity reactions may occur.

4.9 Overdose Terbutaline

Possible symptoms and signs: Headache, anxiety, tremor, nausea, tonic cramp, palpitations, tachycardia, arrhythmia. A fall in blood pressure sometimes occurs.

Laboratory findings; hypokalaemia, hyperglycaemia and lactic acidosis sometimes occur.

Treatment:

Mild and moderate cases: Reduce the dose.

Severe cases: Gastric lavage, administration of activated charcoal. Determination of acid- base balance, blood sugar and electrolytes, particularly serum potassium levels. Monitoring of the heart rate and rhythm and blood pressure. Metabolic changes should be corrected.

A cardioselective beta-blocker (e.g. metoprolol) is recommended for the treatment of arrhythmias causing haemodynamic deterioration. The betablocker should be used with care because of the possibility of inducing bronchoconstriction: use with caution in patients with a history of bronchospasm. If the beta2-mediated reduction in the peripheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given.

Preterm labour: Pulmonary oedema: discontinue administration. A normal dose of loop diuretic (e.g. frusemide) should be given intravenously.

Increased bleeding in connection with Caesarian section: propranolol, 12mg intravenously.

Bromhexine

No symptoms of overdosage have been reported in man to date. If they occur, supportive and symptomatic treatment should be provided.

Guaiphenesin

The effects of acute toxicity from guaifenesin may include gastrointestinal discomfort, nausea and drowsiness. The drug is, however, rapidly metabolised and excreted in the urine. Patients should be kept under observation and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Guaifenesin is an expectorant which decreases the stickiness of mucus (phlegm) and helps in its removal from the airways. Terbutaline is a bronchodilator. It works by relaxing the muscles in the airways and widens the airways. Bromhexine hydrochloride is a mucolytic which thins and loosens mucus (phlegm), making it easier to cough out. Together, they make breathing easier.

5.2 Pharmacodynamic Properties Terbutaline:

Terbutaline is a selective beta2 - adrenergic causing bronchodilation; increase in mucociliary clearance; suppression of oedema and anti-allergic effects.

The pharmacologic effects of beta-adrenergic agonist drugs, including terbutaline, are at least in part, attributable to stimulation through beta-adrenergic receptors on intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Bromhexine:

Bromhexine is an expectorant/mucolytic agent. The drug is a benzylamine derivative (2- amino-3,5-dibromo-N-cyclohexyl N-methylbenzylamine hydrochloride) and also a derivative of vasicine and adhatodic acid, alkaloids obtained from the plant Adhatoda vasica.

Following oral administration, bromhexine has increased sputum volume and reduced the viscosity of bronchial secretions in chronic bronchitis patients. The drug has been reported to induce hydrolytic depolymerization of mucoprotein fibers and stimulate activity of the ciliated epithelium. An increase in lysosomal activity facilitated by bromhexine has been postulated. Improvements in pulmonary function in bronchitis patients appear secondary to easier expectoration.

An effect of bromhexine on increasing sputum concentrations of various antibiotics (eg, oxytetracycline, erythromycin, ampicillin, amoxicillin) has also been reported. However, some of these effects (exocrine stimulation, increased sputum concentrations) have not been confirmed in some studies.

It has been suggested that a metabolite of bromhexine, ambroxol, may contribute to enhanced secretion from exocrine glands during bromhexine administration.

Guaiphenesin:

Guaiphenesin 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 turn enhance respiratory fluid flow. Guaiphenesin produces its expectorant action within 24 hour.

5.3 Pharmacokinetic properties Terbutaline:

Basic parameters have been evaluated in man after oral administration of therapeutic doses, e.g.

Renal clearance (CLR): 1.925/ml/min (males) Renal clearance (CLR): 2.32ml/min (females)

Terminal half-life T½ has been determined after single and multiple dosing (mean values varied between 16-20 h)

Bioavailability:

Food reduces bioavailability following oral dosing (10% on average). Fasting values of 14-15% have been obtained.

Metabolism:

The main metabolite after oral dosing is the sulphate conjugate and also some glucoronide conjugate can be found in the urine.

Bromhexine:

Absorption
Oral, well absorbed. Rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations occur after about 1 hour following oral administration.
Distribution
It is widely distributed to body tissues. Bromhexine is highly bound to plasma proteins. Bromhexine crosses the blood-brain barrier and small amounts cross the placenta.
Metabolism
Bromhexine undergoes extensive first-pass metabolism in the liver: Ambroxol is a metabolite of bromhexine.
Excretion
Bromhexine is excreted primarily in the urine as metabolites. Only small amounts appear as unchanged drug. About 85 to 90% of a dose is excreted in the urine mainly as metabolites. Approximately 70% of an oral dose of bromhexine has been recovered in the urine within 24 hours. Other excretion: faeces, 4%
Elimination Half-life: It has a terminal elimination half-life of 13 to 40 hours
Guaiphenesin:
Absorption:
Guaiphenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information regarding its pharmacokinetics is available. After the administration of 600 mg Guaiphenesin to healthy adult volunteers, the Cmax was

approximately 1.4ug/ml, with tmax occurring approximately 15 minutes after drug administration.
Distribution:
No information is available on the distribution of Guaiphenesin in humans. Metabolism and elimination:
Guaiphenesin 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.
Pharmacokinetics in Renal/Hepatic Impairment:
There have been no specific studies of Guaiphenesin in subjects with renal or hepatic impairment. Caution is therefore recommended when administering this product to subjects with severe renal or hepatic impairment.
6. Non clinical properties
6.1 Animal Toxicology or Pharmacology
Terbutaline:
Studies in laboratory animals (mini pigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histological evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.
Bromhexine:
Bromhexine has a low acute toxicity index. Guaiphenesin:
Animal studies to assess the long-term carcinogenic and mutagenic potential or the effect on fertility in animals or humans have not been performed.

7. Description:
Orange colour clear mentholated liquid, having sweet taste and pleasant flavour.

8. Pharmaceutical particulars

8.1 Incompatibilities:
NA.

8.2 Shelf-life:
24 Months

8.3 Packaging information:
60 ml, 100 ml and 150 ml bottle.

8.4 Storage and handling instructions:
Store below 30°C. Protect from light.

9. Patient Counselling Information
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

What Alkof+ syrup is and what it is used for?
Alkof+ Syrup is a combination of three medicines: Guaifenesin, Terbutaline and Bromhexine, which relieves cough with mucus. Guaifenesin is an expectorant which decreases the stickiness of mucus (phlegm) and helps in its removal from the airways. Terbutaline is a bronchodilator. It works by relaxing the muscles in the airways and widens the airways. Bromhexine is a mucolytic which thins and loosens mucus (phlegm), making it easier to cough out. Together, they make breathing easier.
What you need to know before you take Alkof+ syrup
- Do not take Alkof+ syrup

If you are allergic to any of the other ingredients of this medicine
- Warnings and precautions Children

Do not give this medicine to children under 6 years of age.
Do not exceed the recommended dose. If symptoms persist, consult your doctor.

- How long is the duration of effect?

The effect of this medicine lasts for an average of 24 hours.

- What is the onset of action?

The effect of this medicine can be observed within an hour of oral administration.

- Are there any effects on Driving?

It is not known whether Alkof+ Syrup alters the ability to drive. Do not drive if you experience any symptoms that affect your ability to concentrate and react.

- Are there any pregnancy warnings?

This medicine does not cause any harm to the fetus, but there is no scientific evidence to certify it. Hence, it is best to consult a doctor before consuming it during pregnancy. It is best to be administered orally.

- Is it habit forming?

No habit forming tendencies were reported.

- Are there any breast-feeding warnings?

This medicine is not recommended for use in women who are breastfeeding as it can cause side effects for the baby. Consult your doctor before taking this medication.

How to take Alkof+ syrup
Take this medicine in the dose and duration as advised by your doctor. Check the label for directions before use. Measure it with a measuring cup and take it by mouth. Shake well before use.
Alkof+ Syrup may be taken with or without food, but it is better to take it at a fixed time.

If you take more Alkof+ syrup than you should
Contact your doctor immediately if an overdose is suspected. Symptoms of overdose may include dizziness, restlessness, and confusion. Supportive measures like gastric lavage might be initiated based on the severity of symptoms.
If you forget to take Alkof+ syrup
Take the missed dose as soon as you remember. If it is almost time for the next scheduled dose, then the missed dose can be skipped.

Possible side effects
Most side effects do not require any medical attention and disappear as your body adjusts to the medicine. Consult your doctor if they persist or if you're worried about them

Common side effects of Alkof+ syrup are:

- Nausea
- Diarrhea
- Bloating
- Indigestion
- Vomiting
- Stomach pain
- Sweating
- Dizziness
- Headache
- Skin rash
- Hives
- Tremor
- Increased heart rate

How to store Alkof+ syrup
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date, which is stated on the carton and the blisters after EXP. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects to pvglobal@alkem.com. By reporting side effects you can help provide more information on the safety of this medicine.

10. Details of manufacturer
Manufactured by:
ALKEM LABORATORIES LTD.
At: Village-Thana, Baddi, Distt-Solan, Himachal Pradesh - 173 205.

11. Details of permission or license number with date
M.L.No. L/MNB/06/224 dated 12/04/2016.

12. Date of revision
05/10/2020.

13. Marketed by:

ALKEM
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