Summary of Product Characteristics

1. Name of the medicinal product
BRONCHOPHANE Syrup

2. Qualitative and quantitative composition
Each 5 ml contains:
Guaiphenesin ..... 50 mg
Ephedrine hydrochloride ..... 7.5 mg
Diphenhydramine hydrochloride……..... 5 mg
Dextromethorphan hydrobromide ..... 6.25 mg
Inactive ingredients: (See section 6)

3. Pharmaceutical form
Clear viscous orange yellow syrupy liquid with peach flavor.

4. Clinical particulars
4.1 Therapeutic indications
For the relief of cough (dry and/or chesty), associated congestive symptoms.

4.2 Posology and method of administration
For oral use.
Adults and children aged 12 years and over:
10 ml – 20 ml four times a day.
Children more than 6 years:
5 ml – 10 ml four times a day.
Elderly (over 65 years):
As for adults.
Do not exceed the stated dose.
Keep out of the reach and sight of children.

4.3Contraindications
Known hypersensitivity to the product or any of its constituents.
This product should not be administered to patients currently receiving monoamine oxidase inhibitors (MAOIs) or those patients who have received treatment with MAOIs within the last two weeks.
Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to patients in, or at risk of developing, respiratory failure.
Contraindicated in persons under treatment with selective serotonin reuptake inhibitors (SSRIs)
This product should not be used in liver dysfunction.

Bronchophane should not be administered to patients where cough is associated with asthma, or patients with productive cough.
Diphenhydramine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.
Bronchophane is contraindicated in children less than 2 years, and not to be taken with children less than 6 years without medical supervision.

4.4 Special warnings and precautions for use
This product should not be used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.
Because of the antimuscarinic properties of dextromethorphan and diphenhydramine antihistamine should be used with care in conditions such as closed angle glaucoma, urinary retention, prostatic hyperplasia or pyeloduodenal obstruction. Caution should also be exercised in patients with epilepsy or severe cardiovascular disorders. Caution is needed for the use of dextromethorphan in patients with a history of asthma, or with chronic or persistent cough. This medicine should be used with caution in atopic children due to histamine release.
Subjects with moderate to severe renal dysfunction or urinary retention should exercise caution when using this product.
Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively small doses.
Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors
Avoid alcoholic drink.
Drug dependence, tolerance and potential for abuse:
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).
Drug withdrawal syndrome:
The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Serotonin Syndrome:
Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.
Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, treatment with this product should be discontinued.
Use with caution in patients with diabetes mellitus as possible higher incidence of atherosclerotic disease may increase risk, and ephedrine as a sympathomimetic may affect blood glucose levels.

Ingredients with specified warnings:
Bronchophane contains less than 1mmol sodium (23mg) per dose, that is to say essentially 'sodium-free'.
Bronchophane contains sucrose and sorbitol. Patients with rare hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Sorbitol may cause softening of stool.
Bronchophane contains propylene glycol. **Bronchophane** is contraindicated in pregnant women, patients with renal or hepatic impairment, and in patients treated with metronidazole or disulfiram, because of the potential risk of toxicity from the large amount of the excipient propylene glycol.

4.5 Interaction with other medicinal products

Diphenhydramine-specific interactions:
Diphenhydramine as an antihistamine has additive sedative effects with alcohol and other CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics. It may also have additive antimuscarinic effects with antimuscarinic drugs such as atropine and some antidepressants.
Diphenhydramine as an antihistamine may theoretically antagonise the effect of histamine and betahistine.
Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 and may affect the metabolism of some beta blockers and the anti depressant venlafaxine.
Dextromethorphan-specific interactions:
Avoid use of dextromethorphan with moclobemide or other reversible MAO-A inhibitors; rasagiline or other MAO-B inhibitors.
Manufacturer of memantine advises avoid concomitant use with dextromethorphan.

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.
Cimetidine inhibits the metabolism of opioid analgesics.

CYP2D6 inhibitors:

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, SSRIs (including sertraline), bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Ephedrine hydrochloride- specific interactions:

Antihypertensives: may diminish the effects of ephedrine.
Antipsychotics: may antagonise the hypertensive effects of sympathomimetics.
Caffeine: may enhance the side effects of ephedrine.
Theophylline: concomitant use with ephedrine may potentiate the adverse effects.
Anti-arrhythmic - including beta-blockers and quinidine: ephedrine may increase the risk of arrhythmias, and block the hypotensive effects of beta-blockers.
Adrenergic neuron blockers such as guanethidine: ephedrine may block the hypotensive effects.
Cardiac glycosides such as digoxin: ephedrine may increase the risk of arrhythmias.
Ergotamine and methysergide: ephedrine may increase the risk of ergotism.
Oxytocin: there is increased risk of hypertension when vasoconstrictor sympathomimetics are given with oxytocin.
Doxapram: there is increased risk of hypertension when sympathomimetics are given with doxapram.
Dexamethasone: ephedrine accelerates the metabolism of dexamethasone.
MAO-B inhibitors (such as rasagiline and selegiline): risk of hypertension.
Moclobemide: risk of hypertensive crisis when given with sympathomimetics.
Appetite suppressants and amphetamine-like psychostimulants: risk of hypertension.
Antiparkinsonian drugs: Risk of additive cardiovascular toxicity when some sympathomimetics given with drugs such as levodopa and bromocriptine
Tricyclic antidepressants may reduce the effect of sympathomimetics such as ephedrine hydrochloride and increase the risk of arrhythmias.

4.6 Pregnancy and lactation

Although dextromethorphan and diphenhydramine have been in widespread use for many years, insufficient data are available on their use during pregnancy. Use during pregnancy is inadvisable unless there is a clear need. Caution should, therefore, be exercised by balancing the potential benefits of treatment against any possible hazards.

It is not known if dextromethorphan or its metabolites are excreted in human breast milk. Diphenhydramine is excreted in breast milk but the amount has not been quantified. This product is, therefore, best avoided during breast feeding.

4.7 Effects on ability to drive and to use machines

This preparation may cause drowsiness. If affected, the patient should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive.
• Do not drive until you know how the medicine affects you.
• It is an offence to drive while under the influence of this medicine.
• However, you would not be committing an offence (called “statutory defence”) if:
- The medicine has been prescribed to treat a medical or dental problem.
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

The following undesirable effects have been reported for use of dextromethorphan or sedating antihistamines including diphenhydramine, and may arise from use of this product. The frequency of adverse effects cannot be estimated from available data.

Undesirable effects may be attributable to both dextromethorphan and sedating antihistamines unless otherwise stated.

Blood and Lymphatic system disorders:

Blood disorders including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia (attributable to sedating antihistamines).

Immune system disorders:

Ephedrine hydrochloride: Rash.

Metabolism and Nutrition disorders:

Ephedrine hydrochloride: Anorexia, hyperglycaemia.

Psychiatric disorders:

Confusion, excitation (attributable to dextromethorphan), depression (attributable to sedating antihistamines), drug dependence.
Ephedrine hydrochloride: Anxiety, insomnia, restlessness, excitability, fear, confusion, irritability, psychotic states.

Nervous system disorders:

Drowsiness and lowered ability to concentrate, dizziness, convulsions, extrapyramidal effects, paradoxical stimulation, headache, psychomotor impairment, tremor, paraesthesias, sleep disturbances (attributable to sedating antihistamines).
Ephedrine hydrochloride: Headache, sweating, piloerection, increased salivation.

Eye disorders:

Blurred vision, angle-closure glaucoma (attributable to sedating antihistamines).
Ephedrine hydrochloride: mydriasis

Ear and Labyrinth disorders:

Tinnitus (attributable to sedating antihistamines).

Cardiac disorders:

Palpitations, arrhythmias (attributable to sedating antihistamines).
Ephedrine hydrochloride: Tachycardia, palpitations, arrhythmias

Vascular disorders:

Hypotension (attributable to sedating antihistamines).
Ephedrine hydrochloride: Hypertension, cold extremities

Respiratory, Thoracic and Mediastinal disorders:

Respiratory depression (attributable to dextromethorphan), thickened respiratory tract secretions, bronchospasm (attributable to sedating antihistamines).
Ephedrine hydrochloride: Dyspnoea

Gastrointestinal disorders:

Gastrointestinal disturbances (including nausea, vomiting, diarrhoea), dry mouth (attributable to sedating antihistamines).
Ephedrine hydrochloride: Dry mouth, nausea, vomiting.
Gastro-intestinal discomfort, nausea and vomiting have occasionally been reported with guaifenesin particularly in large doses.

Hepatobiliary disorders:

Liver dysfunction (attributable to sedating antihistamines).

Skin and Subcutaneous tissue disorders:

Hypersensitivity reactions including skin rash, angioedema, sweating, hair loss (attributable to sedating antihistamines).

Musculoskeletal, Connective tissue and Bone disorders:

Myalgia (attributable to sedating antihistamines).
Ephedrine hydrochloride: Muscle tremor, weakness

Renal and Urinary disorders:

Urinary retention (attributable to sedating antihistamines).

Ephedrine hydrochloride: Difficulty in micturition, urinary retention.

General disorders and Administration site conditions:

Anaphylaxis (attributable to sedating antihistamines), drug withdrawal syndrome.

4.9 Overdose

Acute overdose of dextromethorphan does not usually result in serious signs and symptoms unless very large amounts have been ingested. It is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Signs and symptoms of substantial overdose may include nausea and vomiting, CNS disturbances (hyperexcitability, irritability, mental confusion, lethargy, somnolence, ataxia, auditory and visual hallucinations, psychotic disorder), dizziness, slurred speech, nystagmus and respiratory depression.

Symptoms and signs:

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.

In the event of massive overdose, the following symptoms may be observed: coma, respiratory depression, convulsions.

Management:

-Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

-For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

Mild cases of diphenhydramine overdose are mainly characterised by prominent antimuscarinic effects including dry mouth, headache, nausea, tachycardia and urinary retention. Larger doses produce depression or stimulation of the CNS. In small children, the stimulatory effects predominate and clinical features include hallucinations and convulsions. Adults usually develop drowsiness first, then convulse and lapse into coma at later stage. Fever and flushing is seen in children but is uncommon in adults.

Gastric lavage should be used if indicated. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children (0.01mg/kg body weight). Convulsions can be controlled with diazepam. Other treatment is supportive and symptomatic and may include artificial respiration, external cooling for hyperpyrexia and intravenous fluids.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacodynamic properties:

Diphenhydramine:

Diphenhydramine is a potent antihistamine and antitussive with anticholinergic and sedative properties. Recent experiments have shown that the antitussive action is discrete from H_1-receptor blockade and is located in the brain stem.

Antihistamines, like diphenhydramine, are useful for controlling nasal itching, sneezing and rhinorrhoea but are less effective for the relief of nasal congestion.

Guaifenesin:

Guaifenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant.

Dextromethorphan:

Dextromethorphan is a non-opioid, centrally acting cough suppressant. It raises the threshold for the cough reflex in the medulla oblongata. In therapeutic doses, it has no significant analgesic, respiratory depressant, euphoriant or dependence-producing properties. It does not inhibit ciliary function.

Ephedrine:

Ephedrine in therapeutic doses produces peripheral vasoconstriction on the blood vessels of the nasal and sinus mucosa. It reduces the swelling associated with inflammation of the mucous membrane lining the nasal passage, clearing the airway and minimizing the contribution of the post-nasal drip to the irritation and congestion in the lower respiratory tract.

5.2 Pharmacokinetic properties

Dextromethorphan:

Dextromethorphan is rapidly absorbed from the gastrointestinal tract following oral administration. It is subject to extensive presystematic metabolism resulting in very low peak plasma concentrations of 1.8ng/ml within 2.5 hours of an oral dose. Peak concentrations of the main metabolite, dextrophan occur 1-2 hours after ingestion. The terminal plasma elimination half-life of dextrophan is about three hours.

It is not known if dextromethorphan or dextrophan is excreted into breast milk or crosses the placenta.

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (including the cytochrome P450 2D6 isozyme (CYP2D6), which is then conjugated by UDP-glucuronosyl transferases) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-

Nmethylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.
Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.
Less than 1% of the dose of dextromethorphan is excreted in the faeces. Urinary excretion of parent drug and metabolites accounts for up to 50% of the ingested dose over 24 hours.

Diphenhydramine:

Diphenhydramine is well absorbed in the gastro-intestinal tract. Peak serum levels are reached at between 2 - 2.5 hours after an oral dose. Duration of activity is between 4 - 8 hours. The drug is widely distributed throughout the body, including the CNS, and some 78% is bound to plasma proteins. Estimates of the volume of distribution lie in the range 3.3 - 6.8 l/kg.
Diphenhydramine experiences extensive first-pass metabolism, undergoing two successive N-Demethylations; the resultant amine is then oxidised to a carboxylic acid. Values for plasma clearance lie in the range 600 - 1300 ml/min and the terminal elimination half-life lies in the range 3.4 - 9.3 hours. Little unchanged drug is excreted in the urine.
Pharmacokinetic studies in elderly subjects indicate no major differences in drug distribution or elimination compared with younger adults.

Renal Dysfunction:

The results of a review on the use of diphenhydramine in renal failure suggest that in moderate to severe renal failure, the dose interval should be extended by a period dependant on glomerular filtration rate (GFR)

Hepatic Dysfunction:

After intravenous administration of 0.8 mg/kg Diphenhydramine, a prolonged half-life was noted in patients with chronic liver disease which correlated with the severity of the disease. However, the mean plasma clearance and apparent volume of distribution were not significantly affected.

Guaifenesin:

Guaifenesin is readily absorbed after oral administration. It is rapidly metabolised by oxidation to β-(2-methyoxy-phenoxy) lactic acid. About 40% of a dose is excreted as this metabolite in the urine in 3 hours.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium phosphate dibasic, citric acid anhydrous, sucrose, sorbitol 70%, sodium benzoate, Sunset yellow no.6, peach flavor, propylene glycol, ethyl alcohol 4.06 mg, purified water.

6.2 Incompatibilities

None known.

6.3 Special precautions for storage
Store at a temperature not exceeding 30˚C.

6.4 Nature and contents of container
BRONCHOPHANE Syrup: Bottle of 100, 125, 150ml.

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

7. Marketing authorization holder
Egyptian international pharmaceutical industries company (EIPICO)

8. MARKETING AUTHORISATION NUMBER(S)
06217/07583/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24-07-2021

10. Date of revision of the text
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