SUMMARY OF PRODUCT CHARACTERISTICS

Chericof Cough Formula

(Chlorpheniramine Maleate, Dextromethorphan Hydrobromide and Phenylephrine Hydrochloride syrup)

1. NAME OF THE MEDICINAL PRODUCT

Chericof Cough Formula

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chericof Cough Formula
Each 5 ml contains:
Chlorpheniramine Maleate USP……..… 2 mg
Dextromethorphan Hydrobromide USP ……10 mg
Phenylephrine Hydrochloride BP……5 mg
In a pleasantly flavoured syrup……q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications [1-4]

Chericof Cough formula is indicated for symptomatic relief from dry irritating cough, allergic cough and upper respiratory symptoms such as irritation of throat, running nose, nasal congestion and watery eyes associated with allergy or common cold.

4.2 Posology and method of administration [1-8]

Adults and children above 12 years: 10 ml of **Chericof Cough formula** (2 teaspoonfuls), 4 – 6 times a day. Do not exceed 60 ml in any 24 hours or as directed by physician.

Elderly: The elderly are more likely to experience neurological anticholinergic effects of chlorpheniramine. Consideration should be given to using a lower daily dose of chlorpheniramine (e.g. a maximum of 12mg in any 24 hours). Accordingly, adjust the

dose of **Chericof Cough Formula** and do not exceed 30 ml in any 24 hours or as directed by the physician.

Children 6 – 12 years: 5 ml of **Chericof Cough Formula** (1 teaspoonful) every 4 – 6 hours. Do not exceed 30 ml in any 24 hours or as directed by physician.

Children below 6 years: As directed by the physician.

Not recommended in children below 2 years of age.

4.3 Contraindications [1-3, 5]

Chericof Cough formula is contraindicated in patients:

- with known hypersensitivity to antihistamines, dextromethorphan and phenylephrine or to any of the excipients listed in section 6.1
- being treated with monoamine oxidase inhibitors or within 14 days of ceasing such treatment
- with or at risk of respiratory failure
- with liver disease
- taking selective serotonin reuptake inhibitors
- with cardiovascular disease, high blood pressure, diabetes mellitus, closed angle glaucoma, hyperthyroidism, prostatic enlargement and pheochromocytoma

4.4 Special warnings and precautions for use [1-4]

Before prescribing medication to suppress or modify cough, identify and provide therapy for the underlying cause of the cough and take caution that modification of cough does not increase the risk of clinical or physiologic complications.

Do not exceed the single and maximum daily dose. Do not use for longer than 7 days. Overdose may result in serious harm. DO NOT give with any other cough and cold medications since harm may occur, unless recommended by a healthcare practitioner. Consult a healthcare practitioner prior to combining with other medications, including natural health products, prescription drugs or nonprescription drugs.

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 and asthma; hepatic impairment; renal impairment. Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g., increased energy, restlessness, nervousness). Avoid use in elderly patients with confusion. The effects of alcohol may be increased and therefore concurrent use should be avoided.

Dextromethorphan should be used with caution in atopic children due to histamine release. Ask a doctor before use if you suffer from a chronic or persistent cough, if you have asthma or are suffering from an acute asthma attack or where cough is accompanied by excessive secretions. Not to be taken with any other cough and cold medicine. Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

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).

Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

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

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population is poor metabolizer 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 metabolisers of CYP2D6 or use CYP2D6 inhibitors (see **section 4.5**).

Serotonergic effects
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 **Chericof Cough Formula** should be discontinued.

Paediatric population
Serious adverse events may occur in children in case of overdose including neurological disorders. Caregivers should be advised not to exceed the recommended dose.

Phenylephrine containing medicine should be used with caution in patients with occlusive vascular disease including Raynaud's phenomenon.

Children under 2 years should not be given this product. This product should be kept out of the reach of children.

Sore throat warning
If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea, or vomiting, consult a doctor promptly.

Chericof Cough Formula contains 2.7 g of sucrose per 5 ml.
- This should be taken into account in patients with diabetes mellitus.
- Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Long-term use increases the risk of dental caries and it is essential that adequate dental hygiene is maintained.

Chericof Cough Formula contains ….. mg of sodium per 5 ml. This should be taken into consideration by patients on a controlled sodium diet

Chericof Cough Formula contains Ponceau 4R Supra (C.I. No. 16255), methyl and propyl parahydroxybenzoate which may cause allergic reactions.

This product contains methyl and propyl paraben which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction [1-3]

Chlorpheniramine
Concurrent use of chlorpheniramine 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 chlorpheniramine concurrently with these medicines. Chlorpheniramine inhibits phenytoin metabolism and can lead to phenytoin toxicity. The anticholinergic effects of chlorpheniramine are intensified by MAOIs.

Dextromethorphan
Not to be used in patients taking monoamine oxidase inhibitors or within 14 days of stopping treatment as there is a risk of serotonin syndrome (pyrexia, hypertension, arrhythmias) when MAOIs are taken in combination with dextromethorphan.

Severe and sometimes fatal reactions have been reported following administration of dextromethorphan to patients receiving MAOIs as there is a risk of serotonin syndrome (pyrexia, hypertension, arrhythmias) [see **section 4.3**].

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

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, diarrhoea 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, flecaninde and propafenone, 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.

Phenylephrine
Phenylephrine should not be given to patients being treated with monoamine oxidase inhibitors or within 14 days of stopping such treatment. Phenylephrine may enhance the effects of anticholinergic drugs such as tricyclic antidepressants. It may increase the possibility of arrhythmias in digitalised patients and may enhance the cardiovascular effects of other sympathomimetic amines (e.g. decongestants).

This medicine should not be taken together with vasodilators, beta-blockers or enzyme inducers such as alcohol.

4.6 Fertility, pregnancy and lactation [1-3]

Pregnancy

There are no adequate reported data from the use of chlorpheniramine maleate in pregnant women. The potential risk for humans is unknown. Use during the third

trimester may result in reactions in the new-born or premature neonates. Not to be used during pregnancy unless considered essentially by a physician.

There is no or inadequate evidence of the safety of dextromethorphan in human pregnancy and therefore this product should not be used during this period.
The safety of phenylephrine during pregnancy has not been established but in view of a possible association of fetal abnormalities with first trimester exposure to phenylephrine, the use of the product during pregnancy should be avoided. In addition, because phenylephrine may reduce placental perfusion, the product should not be used in patients with a history of pre-eclampsia.

Lactation

Chlorpheniramine 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.

No information is available on the secretion of dextromethorphan into breast milk and it is recommended that dextromethorphan should not be used by breast feeding mothers.

The safety of phenylephrine has not been established during lactation. In view of the lack of data on the use of phenylephrine during lactation, this medicine should not be used during breast- feeding.

4.7 Effects on ability to drive and use machines [1-3]

This medicine can impair cognitive function and can affect a patient's ability to drive safely. The anticholinergic properties of chlorpheniramine may cause drowsiness, dizziness, blurred vision and psychomotor impairment, which can seriously hamper the patients' ability to drive and use machinery. Patients should be warned not to drive or operate machinery, until they know how they react to this medicine.

4.8 Undesirable effects [1-3]

Chlorpheniramine
The following adverse events have been reported with chlorpheniramine.
The following convention has been utilised for the classification of the frequency of adverse reactions: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from available data).
The frequency of some reactions is unknown but likely to be rare or very rare:

Blood and lymphatic system disorders
Unknown: haemolytic anaemia, blood dyscrasias

Immune system disorders:
Unknown: allergic reaction, angioedema, anaphylactic reactions
Metabolism and nutritional disorders:
Unknown: anorexia

Psychiatric disorders:
Unknown: confusion*, excitation*, irritability*, nightmares*, depression

Nervous system disorders*:
Very common: sedation, somnolence
Common: disturbance in attention, abnormal coordination, dizziness, headache

Eye disorders:
Common: blurred vision

Ear and labyrinth disorders
Unknown: tinnitus

Cardiac disorders:
Unknown: palpitations, tachycardia, arrythmias

Vascular disorders:
Unknown: Hypotension

Respiratory, thoracic and Mediastinal disorders:
Unknown: thickening of bronchial secretions

Gastrointestinal disorders:
Common: nausea, dry mouth
Unknown: vomiting, abdominal pain, diarrhoea, dyspepsia

Hepatobiliary disorders:
Unknown: hepatitis including jaundice

Skin and subcutaneous disorders:
Unknown: exfoliative dermatitis, rash, urticaria, photosensitivity,

Musculoskeletal and connective tissue disorders:
Unknown: muscular twitching, muscle weakness.

Renal and Urinary disorders:
Unknown: Urinary retention

General disorders and administration site conditions:
Common: fatigue
Unknown: chest tightness

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

Dextromethorphan
The following side effects may be associated with the use of dextromethorphan; Occasional drowsiness, dizziness, excitation, mental confusion, convulsions, respiratory depression, vomiting, gastrointestinal disturbances (nausea and diarrhoea) and skin reactions including rash.

Psychiatric disorders:
Frequency unknown: Drug dependence (see **section 4.4**)
General disorders and administration site conditions:
Frequency unknown: drug withdrawal syndrome

Phenylephrine
Adverse effects may include tachycardia, cardiac arrhythmias, palpitations, hypertension, nausea, vomiting, headache and occasionally urinary retention in males.

4.9 Overdose [1-3]

No information is available as to specific results of an overdose of this syrup. The signs, symptoms and treatment described below are those of individual components.

Chlorpheniramine
The estimated lethal dose of chlorpheniramine is 25 to 50 mg/kg body weight. Symptoms and signs include sedation, paradoxical stimulation of CNS, toxic psychosis, apnoea, convulsions, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias.

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). Hypotension and arrhythmias should be treated vigorously. CNS

convulsions may be treated with i.v. diazepam. Hemoperfusion may be used in severe cases.

Dextromethorphan
It is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

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."

Phenylephrine
Symptoms of overdosage include irritability, restlessness, palpitations, hypertension, difficulty in micturition, nausea, vomiting, thirst and convulsions. In severe overdosage gastric lavage and aspiration should be performed. Symptomatic and supportive measures should be undertaken, particularly with regard to 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 mesilate. A beta blocker may be required to control cardiac arrhythmias.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties [1-3]

Chlorpheniramine
Chlorpheniramine 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. Chlorpheniramine 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 chlorpheniramine include inhibition of histamine on smooth muscle, capillary permeability and hence reduction of oedema and wheal in hypersensitivity reactions such as allergy and anaphylaxis.

Dextromethorphan
Dextromethorphan is a cough suppressant.

Phenylephrine
Phenylephrine is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without stimulating effects on the central nervous system. The sympathomimetic effect of phenylephrine produces vasoconstriction which in turn relieves nasal congestion.

5.2 Pharmacokinetics properties [1-3]

Chlorpheniramine
Chlorpheniramine has been reported to be well absorbed from the gastro-intestinal tract, following oral administration. The effects have been reported to develop within 30 minutes, are maximal within 1 to 2 hours and last 4 to 6 hours. The plasma half-life has been reported to be 12 to 15 hours. Chlorpheniramine is metabolised to the monodesmethyl and didesmethyl derivatives. About 22% of an oral dose is excreted unchanged in the urine.

Dextromethorphan
Dextromethorphan is well-absorbed from the gastrointestinal tract, metabolised in the liver and excreted as both unchanged drug and demethylated metabolites. Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) 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-N-methylmorphinan), 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 predominated in the blood and urine.

Phenylephrine
Phenylephrine is readily absorbed after oral administration but is subject to extensive presystemic metabolism, much of which occurs in the enterocytes. As a consequence,

systemic bioavailability is only about 40%. Following oral administration, peak plasma concentrations are achieved in 1-2 hours. The mean plasma half-life is in the range 2-3 hours. Penetration into the brain appears to be minimal. Following absorption, the drug is extensively metabolised in the liver. Both phenylephrine and its metabolites are excreted in the urine. The volume of distribution is between 200 and 500 litres, but there are no reported data on the extent of plasma protein binding.

5.3 Preclinical safety data [1-3]

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of this prescribing information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylparaben, propylparaben, disodium edetate, sodium chloride, sucrose, glycerol, xanthan gum, ponceau 4R supra, sodium citrate, menthol, propylene glycol, peppermint flavour, cherry flavour, citric acid monohydrate and purified water.

6.2 Incompatibilities

NA

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperature not exceeding 30$_{o}$C, protected from light.

6.5 Nature and contents of container

Glass Bottle with ROPP cap.

6.6 Special precautions for disposal and other handling

Keep out of reach of children

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Limited

8. MARKETING AUTHORISATION NUMBER(S)

04-2119

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

July 2024

REFERENCES

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