Module I Administrative Information

Product Name: RINOVIL-D SYRUP (Dextromethorphan HBR, Phenylephrine HCL, Chlorpheniramine Maleate Syrup)

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1. **Name of the medicinal product**

RINOVIL -D SYRUP (Dextromethorphan HBR, Phenylephrine HCL, Chlorpheniramine Maleate Syrup)

2. **Qualitative and Quantitative**

Composition Label Claim:

Each 5 ml Contains:

Dextromethorphan Hydrobromide… 15 mg

Phenylephrine Hydrochloride ..... 5 mg

Chlorpheniramine Maleate…..... 2 mg

Flavoured Syrup Base ..... Q.S

Colour : Sunset Yellow

For the full list of excipients, see Section 6.1.

3. **Pharmaceutical form**

Syrup

Description: Orange Coloured Flavoured Syrup.

4. **Clinical Particulars**

4.1 Therapeutic indications

RINOVIL -D SYRUP is a combination of three drugs, namely: Chlorpheniramine maleate, Phenylephrine hydrochloride, and Dextromethorphan hydrobromide. RINOVIL -D SYRUP is a combination medicine belonging to a class of drugs called 'cough and cold preparations' primarily used to treat dry cough. Chlorpheniramine maleate works by blocking the action of histamine, a substance responsible for causing allergic reactions. It helps provide relief from allergy symptoms such as sneezing, running nose, watery eyes, itching, swelling, congestion or stiffness. Phenylephrine hydrochloride is a decongestant that

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helps in shrinking the blood vessels

located in the nasal passage, thereby reducing the stuffy nose. Dextromethorphan hydrobromide works by blocking the transmission of nerve signals from the cough centre in the brain to the muscles that produce cough. Thus, RINOVIL -D SYRUP helps to relieve cough, cold and allergic symptoms.is indicated for its Antihistaminic, decongestant and antitussive actions commonly seen in Upper respiratory tract infections.

4.2 Posology and method of administration

Adults and Children 12 years of age and older: 5 mL every 4 to 6 hours, not to exceed 30 mL in 24 hours.

Children 6 to under 12 years of age: 2.5 mL every 4 to 6 hours, not to exceed 15 mL in 24 hours.

Children 2 to under 6 years of age: 1.25 mL every 4 to 6 hours, not to exceed 7.5 mL in 24 hours. Not recommended for use in children under 2 years of age. In mild cases or in particularly sensitive patients, less frequent or reduced doses may be appropriate and adequate.

4.3 Contraindications

RINOVIL -D SYRUP is contraindicated in patients with the following conditions:

• Patients with hypersensitivity or idiosyncrasy to any of its ingredients.

• Sympathomimetic amines are contraindicated in patients with severe hypertension, severe coronary artery disease, patients on monoamine oxidase (MAO) inhibitor therapy.

• Antihistamines are contraindicated in patients with narrow angle glaucoma, urinary retention, peptic ulcer and during an asthma attack.

• Dextromethorphan should not be used in patients receiving a monoamine oxidase inhibitor (MAOI) or for 2 weeks after stopping the MAOI drug.

4.4 Special warnings and precautions for use

WARNINGS

Do not exceed recommended dosage. Sympathomimetic amines should be used

judiciously and sparingly in patients with hypertension, diabetes, ischemic heart disease, hyperthyroidism, increased intraocular pressure or prostatic hypertrophy (See CONTRAINDICATIONS).

Sympathomimetic amines may produce CNS stimulation with convulsions or cardiovascular collapse with accompanying hypotension. The elderly (60 years and older) are more likely to exhibit adverse reactions.

Antihistamines may cause excitability, especially in children. At doses higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

Administration of dextromethorphan may be accompanied by histamine release and should be used with caution in atopic children.

PRECAUTIONS

General: 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. Dextromethorphan should be used with caution in sedated or debilitated patients and in patients confined to supine positions. Use with caution in patients with hypertension, heart disease, asthma, hyperthyroidism, increased intraocular pressure, diabetes mellitus and prostatic hypertrophy.

Information for Patients:

- Avoid alcohol and other CNS depressants while taking this product.
- Patients sensitive to antihistamines may experience moderate to severe drowsiness.
- Patients sensitive to sympathomimetic amines may notice mild CNS stimulation.
- Antihistamines may impair mental and physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. Patients should be warned accordingly.

4.5 Interaction with other medicinal products and other forms of interaction

- Antihistamines may enhance the effects of Phenytoin, tricyclic antidepressants, barbiturates, alcohol and other CNS depressants.
- MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines.
- Sympathomimetic amines may reduce the antihypertensive effects of reserpine, veratrum alkaloids, methyldopa and mecamylamines.

- Effects of sympathomimetics are increased with MAO inhibitors and beta-adrenergic blockers.
- The cough-suppressant action of dextromethorphan and narcotic antitussives are additive.
- Dextromethorphan is contraindicated with monoamine oxidase inhibitors (MAOI).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Pregnancy Category C. Animal reproduction studies have not been conducted with Ambrella Syrup. It is not known whether these products can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Give to a pregnant woman only if clearly needed.

Lactation:

It is not known whether the drugs in Ambrella Syrup are excreted in human milk. Since many drugs are excreted in human milk and because of the potential for serious side effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the use of these products, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Chlorpheniramine

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System Organ Class	Adverse Reaction	Frequency
Nervous system disorders*	Sedation, somnolence	Very common
	Disturbance in attention, abnormal coordination, dizziness headache	Common
Eye disorders	Blurred Vision	Common
Gastrointestinal disorders	Nausea, dry mouth	Common
	Vomiting, abdominal pain, diarrhoea, dyspepsia	Unknown
Immune system disorders:	Allergic reaction, angioedema, anaphylactic reactions	Unknown
Metabolism and nutritional disorders	Anorexia	Unknown
Blood and lymphatic system disorders	Haemolytic anaemia, blood dyscrasias	Unknown
Musculoskeletal and connective tissue disorders	Muscle twitching, muscle weakness	Unknown
Psychiatric disorders	Confusion*, excitation*, irritability*, nightmares*, depression	Unknown
Renal and urinary disorders	Urinary retention	Unknown
Skin and subcutaneous disorders	Exfoliative dermatitis, rash, urticaria, photosensitivity	Unknown
Respiratory, thoracic and mediastinal disorders	Thickening of bronchial secretions	Unknown
Vascular disorders	Hypotension	Unknown
Hepatobiliary disorders	Hepatitis, including jaundice	Unknown
Ear and labyrinth disorders	Tinnitus	Unknown
Cardiac disorders	Palpitations, tachycardia, arrythmias	Unknown
General disorders and administration site conditions	Fatigue	Common
	Chest tightness	Unknown

Phenylphrine

System organ class	Undesirable effects
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Metabolic disorders
Psychiatric disorders	Nervousness, insomnia
Nervous system disorders	Headache, cerebral haemorrhage, paraesthesia
Eye disorders	Mydriasis, angle-closure glaucoma
Cardiac disorders	Pulmonary oedema, bradycardia, tachycardia, arrhythmia, angina pectoris, palpitations, cardiac arrest
Vascular disorders	Hypotension, dizziness, syncope, flushing
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Vomiting, salivary hypersecretion
Renal and urinary disorders	Dysuria, urinary retention
General disorders and administration site conditions	Extravasation, infusion site necrosis, hyperhidrosis
Investigations	Increased blood pressure, abnormal blood glucose

Dextromethorphan

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)

Psychiatric Disorders	Not known Not known Not known Not known	Agitation Confusional state Drug dependence Insomnia
Nervous System Disorders	Not known Not known Not known Not known	Dizziness Psychomotor hyperactivity Seizure Somnolence
Respiratory, thoracic and mediastinal Disorders	Not known	Respiratory depression
Gastrointestinal Disorders	Not known Not known Not known Not known Not known	Abdominal pain Diarrhoea Gastrointestinal disorder Nausea Vomiting
Skin and Subcutaneous Tissue Disorders	Not known Not known Not known Not known	Angioedema Pruritus Rash Urticaria
General disorders and administration site conditions	Unknown	Drug withdrawal syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)
https://pv.pharmacyboardkenya.org'.

4.9 Overdose

No information is available as to specific results of an overdose of RINOVIL -D SYRUP Syrup. The signs, symptoms and treatments described below are those of H1 antihistamine, ephedrine, and dextromethorphan overdose. Symptoms: Should antihistamine effects predominate, central action constitutes the greatest danger. In the small child, predominant symptoms are excitation, hallucination,

ataxia, incoordination, tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma and death may occur in severe cases. In the adult, fever and flushing are uncommon; excitement leading to convulsions and postictal depression is often preceded by drowsiness and coma. Respiration is usually not seriously depressed; blood pressure is usually stable. Should sympathomimetic symptoms predominate, central effects include restlessness,

dizziness, tremor, hyperactive reflexes, talkativeness, irritability and insomnia. Cardiovascular and renal effects include difficulty in micturition, headache, flushing, palpitation, cardiac arrhythmia, hypertension with subsequent hypotension and circulatory collapse. Gastrointestinal effects include dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea and abdominal cramps Dextromethorphan may cause respiratory depression with a large overdose.

Management of Poisoning

(a) Evacuate stomach as condition warrants. Activated charcoal may be useful.

(b) Maintain a non stimulating environment.

(c) Monitor cardiovascular status.

(d) Do not give stimulants.

(e) Reduce fever with cool sponging.

(f) Treat respiratory depression with naloxone if dextromethorphan toxicity is suspected.

(g) Use sedatives or anticonvulsants to control CNS excitation and convulsions.

(h) Physostigmine may reverse anticholinergic symptoms.

(i) Ammonium chloride may acidify the urine to increase urinary excretion of phenylephrine.

(j) Treatment should consist of symptomatic and supportive measures. The hypertensive effects may be treated with an alpha adrenoreceptor blocking drug, such as phentolamine, 5 to 60 mg

i.v. over 10-30 minutes, repeated as necessary. (k) Further care is symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Antihistamine ATC Code:

N07XX59

Chlorpheniramine maleate: It has H1 antihistaminic activity and mild anticholinergic and sedative effects.

Phenylephrine hydrochloride: It is an oral sympathomimetic amine that acts as

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a decongestant to respiratory tract mucous membranes. While its vasoconstrictor action is similar to that of ephedrine, phenylephrine has less pressor effect in normotensive adults.

Dextromethorphan hydrobromide: It is a non-narcotic antitussive with effectiveness equal to codeine. It acts in the medulla oblongata to elevate the cough threshold. Dextromethorphan does not produce analgesia or induce tolerance, and has no potential for addiction. At usual doses, it will not depress respiration or inhibit ciliary activity.

5.2 Pharmacokinetic properties

Chlorpheniramine maleate:

Chlorpheniramine maleate is almost completely absorbed after administration by mouth, with peak plasma concentrations occurring at about 2.5–6 hours. The drug is widely distributed, including into the CNS, with a volume of distribution of between 1 and 10 L/kg. About 70% of chlorpheniramine in the circulation is protein-bound. Chlorpheniramine undergoes some first- pass metabolism and enterohepatic recycling. Chlorpheniramine is extensively metabolised, principally to inactive desmethylated metabolites, which are excreted primarily in the urine, together with about 35% of unchanged drug. Only trace amounts are excreted in the faeces. The mean elimination half-life has been reported to be about 30 hours, with mean values ranging from 2 to 43 hours.

Phenylephrine hydrochloride:

Phenylephrine is readily absorbed after oral administration but is subject to extensive pre- systemic metabolism, much of which occurs in the enterocytes. Therefore, 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 of 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 data on the extent of plasma protein- binding.

Dextromethorphan hydrobromide:

Dextromethorphan is rapidly metabolized with trace amounts of the parent compound in blood and urine. About one half of the administered dose is

excreted in the urine as conjugated metabolites.

Absorption

Dextromethorphan is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in approximately 2–2.5 hours. The low plasma levels of dextromethorphan suggest low oral bioavailability secondary to extensive first-pass (pre- systemic metabolism) in the liver. The maximum clinical effects occur 5–6 hours after ingestion of dextromethorphan.

Distribution

Dextromethorphan is widely distributed in the human body. Dextromethorphan and its active metabolite, dextrorphan, a reactively taken up and concentrated in brain tissue. It is not known if dextromethorphan or dextrorphan are excreted in breast milk or cross the placenta.

Metabolism

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled Odemethylation (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 demethylatedmorphinan 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 predominates in the blood and urine.

Excretion

Dextromethorphan is primarily excreted via the kidneys as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxy-morphinan are further metabolised by glucuronidation and are eliminated via the kidneys. The elimination half-life of the parent compound is between 1.4 to 3.9 hours; for dextrorphan, it is between 3.4 to 5.6 hours. The half- life of dextromethorphan in poor metabolisers is extremely prolonged, being in the

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range of 45 hours.

5.3 Preclinical safety data

Dextromethorphan Hydrobromide General Toxicology

Acute oral toxicity studies conducted with dextromethorphan report the following LD50 values (mg/kg): mouse, 210 and rat, 116. Acute subcutaneous toxicity with dextromethorphan reports the following LD50 value (mg/kg): mouse, 112. Acute intravenous toxicity with dextromethorphan reports the following LD50 value (mg/kg): rat, 16.3. Repeat dose toxicity studies conducted in rats for 13-weeks' duration at doses up to 100 mg/kg and 27 weeks at 10 mg/kg, and of 14 weeks in dogs by oral gavage at doses up to 4 mg/kg on 5 days per week. The only effect recorded was of reduced body weight gain in the rat 13-week study at the highest dose.

Genetic Toxicology

Dextromethorphan hydrobromide was negative in the bacterial reverse mutation assay (Ames test). Dextromethorphan 39 mg/kg is reported to be negative in an in vivo mouse micronucleus test and comet assay. Dextromethorphan was reported to be negative in an in vitro chromosome aberration assay tested up to 200 µg/mL.

Carcinogenicity

There are no known reports of animal carcinogenicity studies for dextromethorphan. The overall weight of evidence for dextromethorphan and its structural analogues, support the conclusion that this class of phenanthrene-based chemicals, and dextromethorphan, in particular, are not genotoxic in vitro or in vivo.

Teratogenicity

There was no association between dextromethorphan and malformations. Fertility

Mating, gestation, fertility, littering and lactation were studied in rats at doses up to 50 mg/kg and no adverse effects were found.

Chlorpheniramine Maleate

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The antihistaminic potency of chlorpheniramine is confined mainly to its (+)-isomer. The racemate is similarly or slightly more toxic because of the contribution of (-)-isomer. The

toxicity may, therefore, be non- specific, perhaps attributable to local anaesthetic action and the toxic effects (excitation/sedation, coma, convulsions and death) resemble those of other classic H1antihistamines. Toxic doses may cause hypotension attributable to myocardial depression, an effect which is clearer with the (-)-isomer. The experimental data on the carcinogenicity and mutagenicity of chlorpheniramine indicate lack of these adverse effects, but the racemate and the (+)-isomer have shown some embryotoxicity in fertility tests. Effective antihistaminic concentrations of chlorpheniramine in vitro are about 1–10 µg/L and oral doses of 0.2–1 mg/kg antagonise histamine induced bronchospasm in guinea pigs.

6. Pharmaceutical particulars

6.1 List of excipients

Liquid
Glucose BP Citric
Acid (Mono) BP
Saodium Benzoate
BP
Colour Sunset Yellow Suppa SPECI
Sodium Saccharine BP
Sugar BP
Ess Orange Sweet Liquid
SPECI Di Sodium E.D.T.A.
BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a cool & dry place. Protect from light.

6.5 Nature and contents of container

100 ml

7. Marketing Authorisation Holder and Manufacturer Marketing Authorisation Holder:

NATIONAL PHARMACY LTD,

Colchester Park,

P.O Box 17843 - 00500

Nairobi, Kenya.

Manufacturer:

BRUSSELS LABORATORIES PVT. LTD.

33. Changodar Ind. Estate. Sarkhej-Bavla Road,

Changodar, Ahmedabad-382210.

8. Marketing Authorization Number:

H2017/CTD4204/228

9. Date of first Authorization /renewal of the authorization:

-2026 May 18

10 Date of revision of text:

September 2024