Summary Product Characteristics

1. Name of the medicinal product

Dexcolin Syrup (Dextromethorphan HBr, Chlorpheniramine Maleate and Phenylephrine HCl syrup)

2. Qualitative and quantitative composition

Each 5 ml contains:
Dextromethorphan HBr BP. 15 mg
Chlorphenamine Maleate BP. 2 mg
Phenylephrine HCl BP.……..5 mg
For the full list of excipients, see section 6.1

3. Pharmaceutical form

A red coloured clear flavored base syrup

4. Clinical particulars

4.1 Therapeutic indications

Dexcolin Syrup is indicated for the relief of dry cough and upper respiratory symptoms, including nasal congestion associated with allergy or the common cold.

4.2 Posology and method of administration

Posology
Adults: 10 ml thrice daily
Paediatric Patients
Aged 7–12 years: 5 mL thrice daily
Aged 4–6 years: 2.5 mL thrice daily Or as directed by the physician

4.3 Contraindications

Patients with a known hypersensitivity to any of its ingredients DEXCOLIN Syrup is contraindicated in the following:
Patients
•with a hypersensitivity or idiosyncrasy to any of its ingredients.
•with severe hypertension, severe coronary artery disease, high blood pressure, diabetes mellitus, closed-angle glaucoma, hyperthyroidism, prostatic enlargement and phaeochromocytoma and patients on monoamine oxidase inhibitor (MAOi) therapy.
•with narrow-angle glaucoma, urinary retention, peptic ulcer, acute asthma and during an asthma attack.
•receiving a MAOi or for 2 weeks after stopping the MAOi drug. There is a risk of serotonin syndrome with the concomitant use of dextromethorphan and MAOIs and the concomitant use of these medications may cause a rise in blood pressure and hypertensive crisis.
•taking selective serotonin-reuptake inhibitors (SSRIs).
•at risk of developing respiratory failure.
•Premature infants or neonates because of their increased susceptibility to the antimuscarinic effects.

4.4 Special warnings and precautions for use

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.
Do not exceed the recommended dosage. Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes, ischaemic heart disease, hyperthyroidism, increased intraocular pressure or prostatic hypertrophy. Sympathomimetic amines may produce central nervous system (CNS) stimulation with convulsions or cardiovascular collapse with accompanying hypotension. The elderly (aged 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.

Chlorpheniramine maleate should be given with caution to patients with epilepsy, severe cardiovascular disorders, liver disorders, glaucoma, urinary retention, prostatic enlargement, pyloroduodenal obstruction, asthma, bronchitis, bronchiectasis, thyrotoxicosis and severe hypertension.
Special care should be taken when using Chlorpheniramine maleate in children and the elderly as they are more prone to developing neurological anticholinergic effects.
Warning: May cause drowsiness. If affected, do not drive or operate machinery. Avoid alcoholic drinks. Although most antihistamines should be avoided by patients with porphyria, Chlorpheniramine maleate has been used and is thought to be safe.

Drug Dependence, Tolerance and Potential for Abuse

In 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 history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).
Drug Withdrawal Syndrome: The drug withdrawal syndrome is characterized 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, and 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 SSRIs, drugs which impair metabolism of serotonin (including 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 medicine should be discontinued. This product should not be taken with any other cough and cold medicines.
Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses. While taking this product, patients should be advised to avoid alcoholic drinks and consult a healthcare professional prior to taking with CNS depressants.
Dextromethorphan is metabolized 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 metabolisers of CYP2D6 or use CYP2D6 inhibitors.
This product should be used with caution in atopic children due to histamine release.
Phenylephrine should be used with caution in patients with occlusive vascular disease, including Raynaud's phenomenon.
Other Warnings: A physician should be consulted in situations where the patient has heart disease, high blood pressure, thyroid disease, diabetes mellitus, glaucoma, a breathing problem such as chronic bronchitis, a cough that lasts or is chronic, e.g. the type that occurs with asthma, and a cough that occurs with too much phlegm (mucus).
Patients with Hepatic or Renal Impairment: There have been no specific studies of this product in renal or hepatic dysfunction. Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Chlorpheniramine Maleate

Antihistamines may enhance the effects of tricyclic antidepressants, barbiturates,alcohol and other CNS depressants. MAOIs prolong and intensify the anticholinergic effects of antihistamines. Sympathomimetic amines may reduce the antihypertensive effects of reserpine, veratrum alkaloids, methyldopa and mecamylamines. Effects of sympathomimetic are increased with MAOIs and beta-adrenergic blockers.

Dextromethorphan Hydrobromide

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.
Dextromethorphan should not be used concurrently in patients taking MAOIs or within 14days of stopping treatment with MAOIs as there is a risk of serotonin syndrome (pyrexia, hallucinations, gross excitation or coma, hypertension, arrhythmias).

CYP2D6 Inhibitors

Dextromethorphan is metabolised 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 SSRIs such as fluoxetine and 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, 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 Hydrochloride

It should not be given to patients being treated with MAOIs or within 14 days of stopping such treatment. It may enhance the effects of anticholinergic drugs such as tricyclic antidepressants. It may increase the possibility of arrhythmias in digitalised patients. It may also 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

Pregnant Women

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

Lactating Women

It is not known whether the drugs in Dexcolin 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

This medicine can impair cognitive function and can affect a patient's ability to drive safely. Drowsiness is possible and, hence, patients should not drive or operate machinery.

4.8 Undesirable effects

Antihistamines may cause sedation, dizziness, diplopia, vomiting, diarrhoea, dry mouth, headache, nervousness, nausea, anorexia, heartburn, weakness, polyuria and dysuria and, rarely, excitability in children. Urinary retention may occur in patients with prostatic hypertrophy. Sympathomimetic amines may cause convulsions, CNS stimulation, cardiac arrhythmia, respiratory difficulties, increased heart rate or blood pressure, hallucinations, tremors, nervousness, insomnia, pallor and dysuria. Gastrointestinal disturbances may occur including abdominal pain, dyspepsia and anorexia.

Paradoxical CNS stimulation may occur especially in children or after high doses. Skin rashes, including exfoliative dermatitis and photosensitivity reactions, and hypersensitivity reactions, including urticaria, may occur. Other side effects include convulsions, sweating, myalgia, paraesthesia, tinnitus, palpitations, tachycardia, arrhythmias, chest pain, haemolytic anaemia and other blood dyscrasias, extrapyramidal effects, tremor, liver dysfunction, including hepatitis and jaundice, sleep disturbances, including nightmares, depression, hypotension, hair loss, thickening of bronchial secretions and confusional psychosis in the elderly. Dextromethorphan may cause drowsiness, dizziness and gastrointestinal disturbance.

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

No information is available as to specific results of an overdose of chlorpheniramine maleate, phenylephrine hydrochloride and dextromethorphan hydrobromide syrup. The signs, symptoms and treatments described below are those of 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 system 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, diarrhoea and abdominal cramps.

Symptoms

Symptoms may include agitation, confusional state, hallucinations, mixed, psychotic disorder, ataxia, clumsiness, coma, dizziness, dysarthria, lethargy, nystagmus, seizure, serotonin syndrome, somnolence, tremor, CNS depression, miosis, mydriasis, respiratory depression, nausea, vomiting,

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

Treatment should be symptomatic and supportive. Gastric lavage may be of use. Naloxone has been used successfully to reverse central or peripheral opioid effects of dextromethorphan in children (0.01 mg/kg body weight).

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.

Overdosage with chlorpheniramine is associated with antimuscarinic, extrapyramidal, gastrointestinal and CNS effects. In infants and children, CNS stimulation predominates over CNS depression, causing ataxia, excitement, tremors, psychosis, hallucinations and convulsions. Hyperpyrexia may also occur. Other symptoms of overdosage in children include dilated pupils, dry mouth, facial flushing.

Deepening coma and cardiorespiratory collapse may follow, and even death. In adults CNS depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse, including arrhythmias.

In severe overdosage the stomach should be emptied. Activated charcoal has been given as have saline laxatives. Convulsions may be controlled with diazepam or phenytoin, although it has been suggested that CNS depressants should be avoided. Other treatment is supportive and symptomatic and may include artificial respiration, external cooling for hyperpyrexia and intravenous fluids. Vasopressors such as noradrenaline or phenylephrine may be used to counteract hypotension. Forced diuresis, peritoneal dialysis or hemodialysis appear to be of limited benefit.
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. A beta-blocker may be required to control cardiac arrhythmias.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough Suppressant, Opium alkaloids and derivatives. ATC code: R05DA09
Mode of Action:

Dextromethorphan hydrobromide is a non-opioid antitussive drug. It exerts its antitussive activity by acting on the cough centre in the medulla oblongata, raising the threshold for the cough reflex.

Chlorphenamine maleate is a potent antihistamine (H1-antagonist). The actions of chlorphenamine include inhibition of histamine on smooth muscle, capillary permeability and hence reduction of oedma and wheal in hypersensitivity reactions such as allergy and anaphylaxis.

The sympathomimetic effect of phenylephrine hydrochloride produces vasoconstriction which in turn relieves nasal congestion.

Dextromethorphan Hydrobromide

Dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methyl-morphinan. It is a synthetic morphine derivative that, in contrast to its levorotatory isomer, has no significant analgesic, respiratory depressant or physical dependency properties at recommended doses. The onset of antitussive effects is realised within 15 to 30 minutes of oral administration, lasting for approximately 3 to 6 hours.

The major metabolite of dextromethorphan, dextrorphan, binds with high affinity to σ- receptors to produce its antitussive activity without exhibiting the classic opiate effects that occur from binding into μ- and δ-receptors. Dextrorphan also exhibits binding activity at serotonergic receptors and was shown to enhance serotonin activity by inhibiting the reuptake of serotonin. In larger than therapeutic doses, dextrorphan is also an antagonist of N-methyl- D-aspartate (NMDA)receptors.

Chlorpheniramine Maleate

Chlorpheniramine competitively antagonises the effects of histamine on H1-receptors and has weak antimuscarinic and moderate anti-serotonin and local anaesthetic actions. It penetrates the brain and causes stimulation or sedation in animals. Chlorphenamine also has anticholinergic activity.

Phenylephrine Hydrochloride

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 CNS. The sympathomimetic effect of phenylephrine produces vasoconstriction, which, in turn, relieves nasal congestion.

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 well-absorbed from the gastrointestinal tract, metabolised in the liver, and excreted as both unchanged drug and demethylated 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 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 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 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 200µg/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
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 1–10µg/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

Flavour

Raspberry
Special Flavour
Cool mint
S 1111 Colour
Ponceau 4R
Sodium Methyl
Hydroxybenzoate
Sodium Propyl
Hydroxybenzoate
Glycerin
Sucrose
Liquid Glucose
Citric Acid Monohydrate
Sodium Benzoate
Sucralose
Flavour Mixed Fruit
1038
Disodium EDTA
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3years.

6.4 Special precautions for storage
Store below 30°C.Protected from direct sunlight Keep all medicines out of reach of children.

6.5 Nature and contents of container
100ml Amber coloured PET bottle , packed in a unit boxes, with literature insert.

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

7.0 Marketing authorisation holder
NEURON PHARMA PVT. LTD.

8.0 Marketing Authorization Number
H2024/CTD10338/23092

9.0 Date of first authorization/renewal of the authorization
2024 September 15

10.0 Date of revision of the text
2024 September 15