Summary of Product Characteristics

1. Name of the medicinal product

AMBRELLA-D Syrup

2. Qualitative and quantitative composition

Each 5 ml contains:

Dextromethorphan Hydrobromide BP 10 mg

Chlorphenamine Maleate BP 2 mg

Phenylephrine Hydrochloride BP 5 mg

Excipients with known effect:

Sucrose 2050 mg

Propylene glycol 300.0 mg

Aspartame 15.00 mg

Sorbitol solution 70% 250 mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral liquid

A green colour Flavoured syrup.

4. Clinical particulars

4.1 Therapeutic indications

Ambrella D is a combination of three drugs, namely: Chlorpheniramine maleate, Phenylephrine hydrochloride, and Dextromethorphan hydrobromide. Ambrella D 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 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, Ambrella D helps to relieve cough, cold and allergic symptoms.

4.2 Posology and method of administration

Adults and Children 12 years of age and older:

1 teaspoonful (5 mL) every 4 to 6 hours, not to exceed 6 teaspoonfuls in 24 hours.

Children 6 to under 12 years of age:

1/2 teaspoonful (2.5 mL) every 4 to 6 hours, not to exceed 3 teaspoonfuls in 24 hours.

Children 2 to under 6 years of age:

1/4 teaspoonful (1.25 mL) every 4 to 6 hours, not to exceed 1.5 teaspoonfuls in 24 hours. Not recommended for us e 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. Or as directed by the physician.

4.3 Contraindications

Ambrella D 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 and 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. 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 Drug Interactions

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'srisk 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 andthioridazine 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

Pregnancy

Animal reproduction studies have not been conducted with Ambrella D 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.

Breast-feeding

It is not known whether the drugs in Ambrella D 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

Ambrella D may cause dizziness or drowsiness in some people. Therefore, drive only if you are alert after taking Ambrella D.

4.8 Undesirable effects

Antihistamines may cause sedation, dizziness, diplopia, vomiting, diarrhea, 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. Dextromethorphan may cause drowsiness, dizziness and GI disturbance.

Reporting of suspected adverse reactions: 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 Ambrella D Syrup. The signs, symptoms and treatments described below are those of H 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.

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

(b) Maintain a nonstimulating 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) Further care is symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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 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 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

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

Bronopol

Sodium benzoate

Sucrose

Propylene glycol

Aspartame

Citric acid

Sorbitol solution 70%

Brilliant blue FCF

Menthol Q.S.

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C protected from sunlight and moisture.

6.5 Nature and contents of container

Bottle of 100 ml

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing Authorization Holder

Lexine Technochem Pvt. Ltd.
202 BBC Tower,
Opp World Trade Centre,
Sarod, Sayajiganj,
Vadodara, Gujarat 390007, India

8. Marketing Authorization Number

H2022/CTD9833/22474

9. Date of first authorization/renewal of the authorization

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10. Date of revision of the text

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