SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Emzolyn 4 Way Syrup

(Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride & Chlorpheniramine Maleate Syrup)

2. Qualitative and quantitative composition

Each 5ml Contains:

Dextromethorphan Hydrobromide BP…….10 mg

Phenylephrine Hydrochloride BP…….....5 mg

Chlorpheniramine Maleate BP……2 mg

Excipient(s) with known effects

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Oral liquid.

Orange colour clear liquid having pleasant flavor.

4. Clinical particulars

4.1 Therapeutic indications

Emzolyn 4 Way syrup is indicated for the symptomatic relief of dry, irritating, or allergic cough, and upper respiratory tract symptoms associated with the common cold or upper respiratory allergies. These symptoms may include:

- Throat irritation
- Nasal congestion
- Rhinorrhea (runny nose)
- Sneezing
- Watery eyes

4.2 Posology and method of administration

Posology

Adults and adolescents (12 years and older):

10 mL to be taken 4 to 6 times daily.

Maximum daily dose: Do not exceed 60 mL in 24 hours, or as directed by the physician.

Elderly:
Elderly patients may be more susceptible to the anticholinergic side effects of chlorpheniramine (e.g., dizziness, confusion, dry mouth, urinary retention).
A reduced dose is advised, with consideration given to limiting the chlorpheniramine intake to a maximum of 12 mg per day.
Recommended dose: Adjust the single dose accordingly; total daily intake should not exceed 30 mL in 24 hours, or as directed by the physician.

Children 6 to 12 years of age:
5 mL every 4 to 6 hours.
Maximum daily dose: Do not exceed 30 mL in 24 hours, or as directed by the physician.

Children below 6 years of age:
Use only under medical supervision.

Not recommended for children under 2 years of age.

Special Population

Paediatric Population

The safety and efficacy of this formulation in neonates and children under 2 years of age have not been established. Therefore, use in this age group is not recommended see Section 4.2.

Geriatric Population

In elderly patients with normal renal and hepatic function, dose adjustment is generally not required. However, due to the increased likelihood of decreased renal function with age, caution is advised.
Renal function should be monitored where appropriate, and dose adjustments may be necessary to reduce the risk of adverse reactions.

Renal Impairment

Dextromethorphan, chlorpheniramine, and phenylephrine are primarily excreted via the kidneys. In patients with impaired renal function, clearance may be reduced, leading to elevated plasma concentrations and increased risk of toxicity. Use with caution in patients with severe renal impairment, with close monitoring for signs of adverse effects.

Hepatic Impairment

Due to the extensive hepatic metabolism of all three active ingredients, caution is advised in patients with moderate to severe hepatic impairment. Dose adjustment and careful monitoring may be required.

Method of Administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Concurrent use with monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing MAOI therapy, due to the risk of hypertensive crisis.
- Use in patients receiving other sympathomimetic agents, due to the risk of additive cardiovascular effects.
- Patients with significant cardiovascular disorders, including severe coronary artery disease and arrhythmias.
- Patients with hypertension, peripheral vascular disease, or hyperthyroidism.
- Presence of closed-angle glaucoma or urinary retention.
- Known or suspected pheochromocytoma.
- Use in patients currently taking selective serotonin reuptake inhibitors (SSRIs), due to the potential risk of serotonin syndrome.
- Dextromethorphan-containing products should not be administered to individuals with or at risk of developing respiratory failure.

4.4 Special warnings and precautions for use

Warnings

- Sympathomimetic agents, such as phenylephrine, should be used with caution and in limited quantities in patients with underlying conditions including hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, elevated intraocular pressure, and prostatic hypertrophy.

- These agents may induce central nervous system stimulation, which in severe cases can result in convulsions or cardiovascular collapse with hypotension.

- Dextromethorphan may promote histamine release and should therefore be used cautiously in atopic children.

Precautions

- Before initiating treatment to suppress or alter the cough reflex, it is essential to identify and manage the underlying cause of the cough. Suppression of cough without addressing the cause may lead to clinical or physiological complications, particularly in patients with chronic respiratory conditions.
- Use with caution in individuals with:
  - Hypertension
  - Cardiovascular disease
  - Bronchial asthma
  - Hyperthyroidism
  - Elevated intraocular pressure (e.g., glaucoma)
  - Diabetes mellitus
  - Prostatic hypertrophy

Patient Information

- Patients should be advised to avoid alcohol and other central nervous system depressants during therapy.
- Individuals who are sensitive to antihistamines may experience moderate to severe drowsiness.
- Those sensitive to sympathomimetic agents may experience mild CNS stimulation.
- Antihistamines may impair the ability to perform potentially hazardous activities, such as driving or operating machinery. Patients should be cautioned accordingly.

4.5 Interaction with other medicinal products and other forms of interaction
Potential for amitriptyline to affect other medicinal products

<u>Chlorpheniramine</u>

i. Concomitant use with hypnotics or anxiolytics may enhance sedative effects. Similar potentiation may occur with alcohol; patients should seek medical advice before combining such substances.

ii. Chlorpheniramine inhibits the metabolism of phenytoin, which may lead to phenytoin toxicity.

iii. Monoamine oxidase inhibitors (MAOIs) potentiate the anticholinergic effects of chlorpheniramine, and concurrent use is contraindicated (see section 4.3).

Dextromethorphan

i. Concurrent administration with MAOIs, or use within 14 days of discontinuing MAOIs, is contraindicated due to the risk of serotonin syndrome, which may present as hyperthermia, hypertension, arrhythmias, agitation, and confusion. Severe and potentially fatal reactions have been reported.

ii. Dextromethorphan may exhibit additive CNS depressant effects when used with alcohol, antihistamines, psychotropic agents, or other CNS depressants.

iii. Dextromethorphan undergoes extensive first-pass metabolism via the CYP2D6 enzyme pathway.
Concomitant use with potent CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, quinidine, terbinafine) can lead to significantly elevated plasma concentrations, increasing the risk of neurotoxicity and serotonin syndrome.

   a. In particular, quinidine has been shown to increase plasma levels of dextromethorphan up to 20-fold, significantly increasing the likelihood of CNS-related adverse effects.

   b. Other inhibitors include: amiodarone, flecainide, propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine, and thioridazine.

iv. If concomitant use with CYP2D6 inhibitors is unavoidable, close monitoring is recommended, and dose adjustment of dextromethorphan may be required.

Phenylephrine

i. Phenylephrine is contraindicated with monoamine oxidase inhibitors (MAOIs) or within 14 days of their withdrawal (see section 4.3).

ii. It may potentiate the anticholinergic effects of drugs such as tricyclic antidepressants.

iii. Use may increase the risk of arrhythmias in patients receiving digitalis glycosides.

iv. It may enhance cardiovascular effects of other sympathomimetic agents, such as nasal decongestants.

v. Concomitant use with vasodilators, beta-blockers, or enzyme inducers (including alcohol) should be avoided due to the risk of adverse cardiovascular events or reduced efficacy.

4.6 Fertility, pregnancy and lactation
Pregnancy

This medicinal product is classified as Pregnancy Category C.

There are no adequate or well-controlled studies in pregnant women. It is not known whether the use of chlorpheniramine, phenylephrine, or dextromethorphan during pregnancy may cause fetal harm or affect reproductive capacity.
Therefore, the product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and only under the supervision of a healthcare professional.

Lactation

It is unknown whether chlorpheniramine, phenylephrine, or dextromethorphan, or their metabolites, are excreted in human breast milk. However, as many drugs are known to pass into breast milk and due to the potential for serious adverse effects in breastfed infants, a risk-benefit assessment should be made.

A decision should be made whether to discontinue breastfeeding or to discontinue the medicine, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines
Phenylephrine has no known adverse effects on the ability to drive or operate machinery.
However, dextromethorphan may impair cognitive and psychomotor function, potentially affecting a patient's ability to drive safely.
Chlorpheniramine, due to its anticholinergic properties, may cause drowsiness, dizziness, blurred vision, and psychomotor impairment, all of which can seriously affect performance in tasks requiring alertness, such as driving or operating machinery.
Patients should be warned not to drive or operate machinery if they experience dizziness, sedation, or visual disturbances.

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.

4.9 Overdose

Dextromethorphan Hydrobromide

Symptoms:

- Nausea and vomiting
- CNS depression
- Dizziness
- Dysarthria (slurred speech)
- Nystagmus
- Somnolence/drowsiness
- Excitation
- Mental confusion
- Psychosis
- Respiratory depression

Management:

- Treatment is symptomatic and supportive.
- Gastric lavage may be beneficial, especially if performed soon after ingestion.
- Naloxone has been used successfully as a specific antidote in children with dextromethorphan toxicity.

Chlorpheniramine Maleate

Symptoms:

- Estimated lethal dose: 25–50 mg/kg body weight
- Antimuscarinic, extrapyramidal, gastrointestinal, and CNS effects
- In children:
    a. Predominantly CNS stimulation, including:
        i. Ataxia
        ii. Excitement
        iii. Tremors
        iv. Psychosis
        v. Hallucinations
        vi. Convulsions
        vii. Hyperpyrexia
        viii. Dilated pupils

ix. Dry mouth
x. Facial flushing

- *In adults:*
  a. Predominantly CNS depression, including:
     i. Drowsiness
     ii. Coma
     iii. Convulsions
     iv. Respiratory failure
     v. Cardiovascular collapse (including arrhythmias)

Management:

- Stomach evacuation should be considered in severe overdose.
- Activated charcoal may be effective if administered within one hour of ingestion.
- Convulsions may be treated with intravenous diazepam or phenytoin; however, CNS depressants should generally be avoided.
- Supportive measures may include:
  - Artificial respiration
  - External cooling for hyperpyrexia
  - Intravenous fluids
  - Vasopressors (e.g., noradrenaline or phenylephrine) for hypotension
- Forced diuresis, peritoneal dialysis, or haemodialysis offer limited benefit.
- Haemoperfusion may be considered in severe cases.

Phenylephrine Hydrochloride

Symptoms:

- Hypertension
- Possible reflex bradycardia
- In severe cases:
  - Confusion
  - Hallucinations
  - Seizures
  - Arrhythmias

Management:

- Early gastric lavage may be considered.
- Provide supportive and symptomatic care.
- Hypertension may be treated with an α-adrenergic blocker (e.g., phentolamine mesylate, 6–10 mg IV).
- Bradycardia may be treated with atropine, preferably after blood pressure is controlled.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistaminic, decongestant and antitussive actions.
ATC CODE: Dextromethorphan Hydrobromide R05DA09, Phenylephrine HydrochlorideR01BA53, Chlorpheniramine Maleate R06AB04.

Mechanism of action

Dextromethorphan Hydrobromide
Dextromethorphan, synthetic derivative of morphine, dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methylmorphinan. Unlike its levorotatory counterpart, it lacks significant analgesic, sedative, or respiratory depressant effects at recommended dosages. Dextromethorphan is a non-opioid antitussive (cough suppressant) drug. It exerts its antitussive activity by acting on the cough centre in the medulla oblongata, raising the threshold for the cough reflex.

Chlorpheniramine Maleate
Chlorpheniramine, an antihistamine of the H1 receptor antagonist class, chlorpheniramine also exhibits anticholinergic properties. It mitigates histamine-induced symptoms such as nasal congestion and sneezing by competitively inhibiting histamine at H1 receptor sites, thereby reducing capillary dilation and mucosal edema.

Phenylephrine Hydrochloride
A sympathomimetic amine, phenylephrine acts primarily as a selective α1-adrenergic receptor agonist. This action leads to vasoconstriction of the nasal mucosa, thereby alleviating nasal congestion. Its decongestant effect is attributed to direct stimulation of α1 receptors, resulting in reduced blood flow and subsequent shrinkage of swollen nasal tissues.

5.2 Pharmacokinetic properties

Dextromethorphan Hydrobromide

- Absorption: Rapidly absorbed from the gastrointestinal tract; peak plasma concentrations are reached within approximately 2 to 2.5 hours.
- Distribution: Widely distributed throughout the body; both dextromethorphan and its active metabolite, dextrorphan, are concentrated in brain tissue.

- Metabolism: Undergoes extensive first-pass metabolism in the liver, primarily via the cytochrome P450 enzyme CYP2D6, converting it into dextrorphan. Other metabolites include 3-hydroxy-N-methylmorphinan and 3-methoxymorphinan.
- Excretion: Primarily excreted via the kidneys as unchanged dextromethorphan and its metabolites. The elimination half-life is approximately 1.4 to 3.9 hours; in poor metabolizers, it may be extended up to 45 hours.

Chlorpheniramine Maleate

- Absorption: Almost completely absorbed after oral administration in the gastrointestinal tract; peak plasma concentrations occur within 2.5 to 6 hours.
- Distribution: Widely distributed, including passage into the central nervous system; approximately 70% is protein-bound in circulation.
- Metabolism and Excretion: Undergoes first-pass metabolism and enterohepatic recycling. Extensively metabolized to inactive desmethylated metabolites, excreted primarily in urine, with about 35% unchanged drug.

Phenylephrine Hydrochloride

- Absorption: Rapidly absorbed from the gastrointestinal tract; however, undergoes extensive first-pass metabolism, resulting in an oral bioavailability of approximately 38%. Peak plasma concentrations are achieved within 1 to 2 hours.
- Distribution: Penetration into the brain is minimal. The steady-state volume of distribution is approximately 340 L.
- Metabolism and Excretion: Metabolized in the liver and intestines by monoamine oxidase A and B, and sulfotransferase enzymes, producing inactive metabolites. Approximately 86% is excreted in urine, with 3 to 16% unchanged drug. The elimination half-life is approximately 2.5 to 3 hours.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients
Menthol

Sorbitol Solution 70% (NC)

Xanthan Gum

Sodium Benzoate

EDTA Sodium

Glycerine

Propylene Glycol

Sodium Chloride

Citric Acid Monohydrate

Neotame

Sucralose

Colour Sunset Yellow FCF

Flavour Mix Fruit (BB12) Blooming Buds

Flavour BTM

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store below 30ºC. Protect from Light. Keep out of the reach of Children.

6.5 Nature and contents of container
Primary Packing:100 ml Orange Transparent Round Pet Bottle.

Secondary Packing: Carton Containing 100 ml Orange Transparent Round Pet Bottle along with its pack insert.

6.6 Special precautions for disposal and other handling
Not Applicable.

7. Marketing authorisation holder
Emzor Pharmaceutical Industries Limited

No 10 Kolawole Shonibare Street,Ajao Estate,Lagos

8. Marketing authorisation number(s)

N/A

9. Date of first authorisation/renewal of the authorisation

N/A

10. Date of revision of the text

N/A