madras pharma

SUMMARY OF PRODUCT CHARACTERISTICS:

1. Name of finished pharmaceutical product:

ZEFCOLIN (Syrup of Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride and Cetirizine Hydrochloride)

1.1. Strength (composition):

Each 5 ml contains:

Dextromethorphan Hydrobromide	BP	10 mg
Phenylephrine Hydrochloride	BP	5 mg
Cetirizine Hydrochloride	BP	5 mg
Menthol	USP	1.5mg

1.2. Pharmaceutical dosage form:

Cough Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

2.1 Qualitative Declaration:

S.No	Ingredients	Specification	Therapeutic Category
1	Dextromethorphen Hydrobromide	BP	Active Ingredient
2	Phenylephrine Hydrochloride	BP	Active Ingredient
3	Cetirizine Hydrochloride	BP	Active Ingredient
4	Menthol	USP	Active Ingredient
5	Sucrose	BP	Sweetner
6	Glycerine	BP	Sweetner
7	Propylene Glycol	BP	Solubilizer
8	Sodium Benzoate	BP	Preservative
9	Bronopol	BP	Preservative
10	Di Sodium EDTA	BP	Chelating Agent
11	Sodium Citrate	BP	Alkalizer
12	Tartazine Yellow Supra	IH	Colourant
13	Sweet orange Flavour 618	IH	Flavouring
14	Mixed Fruit Flavour 1038	IH	Flavouring
15	Pine Apple Flavour No .1	IH	Flavouring
16	Bittermask Flavour No .1	IH	Flavouring
17	Purified Water	BP	Vehicle

2.2 Quantitative Declaration:

Batch size: 3300 Litres

S. No.	Ingredients	Label claim (mg)	OA in %	Added mg/ 5 ml	Added kg/ Batch	Specifi-cation
1.	Dextromethorphen Hydrobromide	10mg	2%	10.20	6.732	BP
2.	Phenylephrine Hydrochloride	5mg	2%	5.10	3.366	BP
3.	Cetirizine Hydrochloride	5mg	2%	5.10	3.366	BP
4.	Menthol	1.5mg	5%	1.58	1.040	USP
5	Sucrose	---	--	3000.00	1980.000	BP
6.	Glycerine	---	--	750.00	495.000	BP
7.	Propylene Glycol			250.00	165.000	BP
8.	Sodium Benzoate	---	--	2.50	1.650	BP
9.	Bronopol	---	--	0.25	0.167	BP
10.	Di Sodium EDTA	---	--	2.50	1.650	BP
11.	Sodium Citrate	---	--	3.00	1.980	BP
12.	Tartazine Yellow Supra	---	--	0.25	0.167	IH
13.	Sweet orange Flavour 618	---	--	20.00	13.200	IH
14.	Mixed Fruit Flavour 1038	---	--	10.00	6.600	IH
15.	Pine Apple Flavour No .1	---	--	10.00	6.600	IH
16.	Bittermask Flavour No .1	---	--	12.50	8.250	IH
17.	Purified Water	---	--	q.s	q.s	BP

Abbreviation:

USP : United States Pharmacopoeia

BP : British Pharmacopoeia

IH : In-House

*** -** Qty of Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Cetirizine Hydrochloride shall be dispensed based on Assay and LOD

2.3 Salts and Hydrates

Not Applicable

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral Powders for solution or suspension

Not Applicable

2.6 Parenterals excluding powders for reconstitution

Not Applicable

2.7 Powders for reconstitution prior to parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal Patches

Not Applicable

2.10 Multidose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

Not Applicable

3. PHARMACEUTICAL FORM

Yellow coloured clear syrupy liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zefcolin is indicated for symptomatic relief of dry unproductive cough due to post nasal drip, allergic & vasomotor rhinitis, allergic pharyngitis, laryngitis & sinusitis, allergic cough following URTI and surgery

4.2 Posology and method of administration

5-10ml, 2-3 times a day or as directed by the Physician

4.3 Method of Administration

As directed by the Physician

4.4 Contraindications

Contraindicated in patients with pre-existing cardiac tachyarrhythmias.

Hypersensitivity to Guaifenesin. And in conditions like Seizures, Hypersensitivity to murine proteins.

4.5 Special warnings and precautions for use

Should not be administered to patients with chronic or persistent cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.

Administer drug with extreme caution to patients with hyperthyroidism, bradycardia, partial heart block, myocardial disease, prostatic hypertrophy, diabetes mellitus, increased IOP, or severe arteriosclerosis; trouble urinating due to enlarged prostate gland.

4.6 Paediatric Population

Not Applicable

4.7 Interaction with other medicinal products and other forms of interaction

Dextromethorphan Hydrobromide: The concomitant use of a dextromethorphan-containing product and monoamine oxidase inhibitors can occasionally result in symptoms such as hyperpyrexia, hallucinations, gross excitation or coma.

Phenylephrine Hydrochloride: Concurrent use may enhance the pressor effects and induce tachycardia, especially in infants. Decrease phenylephrine's effect. Arrhythmias.

Cetirizine Hydrochloride: No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin.

Menthol: Menthol should be used only if clearly needed during pregnancy.

4.8 Additional information on special populations

Not Applicable

4.9 Paediatric Population

Not Applicable

4.10 Fertility, Pregnancy and lactation

Dextromethorphan Hydrobromide: It should therefore only be used when the potential benefit of treatment to the mother exceeds any possible hazards to the developing foetus or suckling infant.

Phenylephrine Hydrochloride

Pregnancy: Category C.

Lactation: Undetermined.

Cetirizine Hydrochloride:

Pregnancy: Category B: In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively

Nursing Mothers: In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg

Menthol: Menthol should be used only if clearly needed during pregnancy.

4.11 Effects on ability to drive and use machines

Dextromethorphan Hydrobromide : This medicine may make you feel drowsy or dizzy. If you are affected do not drive or use machines. The risk of these effects is increased with alcohol and some other medicines.

Cetirizine Hydrochloride: Cetirizine Hydrochloride does not usually cause drowsiness when taken at the recommended dose, however patients should be warned not to drive or operate machinery if any effects are apparent.

4.12 Undesirable effects

Side effects attributed to dextromethorphan are uncommon; occasionally dizziness, nausea, vomiting, or gastro-intestinal disturbance may occur. Respiratory difficulty, Dysuria; urinary retention. Anorexia, flushing, increased salivation, urinary retention.

4.13 Overdose

Overdose may include drowsiness, lethargy, nystagmus, ataxia, respiratory depression, nausea, vomiting, hyperactivity. Coma, hypotension, profuse sweating, sedation, sensation of fullness in head, severe hypertension, shock, short paroxysms of ventricular tachycardia, somnolence, tingling of extremities, ventricular extrasystoles, vomiting.

5. PHARMACOLOGICAL PROPERTIES

A. Dextromethorphan Hydrobromide

Pharmacology

Pharmacodynamic Properties

Dextromethorphan 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. A single oral dose of 10-20 mg dextromethorphan produces its antitussive action within 1 hour and lasts for at least 4 hours.

Pharmacokinetics

Absorption

Dextromethorphan is well absorbed from the gut following oral administration. Due to individual differences in the metabolism of dextromethorphan, pharmacokinetic values are highly variable. After the administration of a 20 mg dose of dextromethorphan to healthy volunteers, the Cmax varied from < 1 mg/l to 8 mg/l, occurring within 2.5 hours of administration.

Distribution

Due to extensive pre-systemic metabolism by the liver, detailed analysis of the distribution of orally administered dextromethorphan is not possible.

Metabolism and Elimination

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation 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 dextrophan (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.

Preclinical safety data

Chronic and subchronic toxicity

Subchronic and chronic toxicity studies carried out in the dog and rat revealed no evidence of any toxic effects specific to dextromethorphan.

Mutagenic and tumorigenic potential

Dextromethorphan hydrobromide has not been adequately studied with respect to its mutagenic potential. A bacterial test for point mutations was negative. The mutagenic potential cannot be adequately assessed. No long-term animal studies have been conducted to determine the tumorigenic potential.

Reproductive toxicity

Studies on embryotoxicity, perinatal/postnatal toxicity and fertility in the rat have shown negative results up to a dose of 50 mg/kg/day.

B. Phenylephrine Hydrochloride

Pharmacology

Phenylephrine hydrochloride produces vasoconstriction that lasts longer than that of epinephrine and ephedrine. Responses are more sustained than those of epinephrine, lasting 20 minutes after intravenous and as long as 50 minutes after subcutaneous injection. Its action on the heart contrasts sharply with that of epinephrine and ephedrine, in that it slows the heart rate and increases the stroke output, producing no disturbance in the rhythm of the pulse.

Phenylephrine is a powerful postsynaptic alpha-receptor stimulant with little effect on the beta receptors of the heart. In therapeutic doses, it produces little if any stimulation of either the spinal cord or cerebrum. A singular advantage of this drug is the fact that repeated injections produce comparable effects.

The predominant actions of phenylephrine are on the cardiovascular system. Parenteral administration causes a rise in systolic and diastolic pressures in man and other species. Accompanying the pressor response to phenylephrine is a marked reflex bradycardia that can be blocked by atropine; after atropine, large doses of the drug increase the heart rate only slightly. In man, cardiac output is slightly decreased and peripheral resistance is considerably increased. Circulation time is slightly prolonged, and venous pressure is slightly increased; venous constriction is not marked. Most vascular beds are constricted; renal, splanchnic, cutaneous, and limb blood flows are reduced but coronary blood flow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised.

The drug is a powerful vasoconstrictor, with properties very similar to those of norepinephrine but almost completely lacking the chronotropic and inotropic actions on the heart. Cardiac irregularities are seen only very rarely even with large doses.

C. Cetirizine Hydrochloride

Pharmacology

Pharmacodyanamics

Mechanism of Action: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. in vivo and ex vivo animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. In vitro receptor binding studies have shown no measurable

affinity for other than H1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H1 receptors.

Pharmacokinetics

Absorption: Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of tablets, chewable tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. Comparable bioavailability was also found between the cetirizine tablet and the cetirizine chewable tablet taken with or without water. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (Cmax) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of exposure (AUC) of the cetirizine tablet or chewable tablet, but Tmax was delayed by 1.7 hours and 2.8 hours respectively, and Cmax was decreased by 23% and 37%, respectively in the presence of food.

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

Metabolism: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Elimination: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min

D. Menthol

Pharmacology

Pharmacodyanamics

Menthol is a covalent organic compound made synthetically or obtained from peppermint or other mint oils. Menthol's ability to chemically trigger cold-sensitive receptors in the skin is responsible for the well known cooling sensation that it provokes when inhalated, eaten, or applied to the skin. It should be noted that menthol does not cause an actual drop in temperature.

Mechanism of action

Menthol primarily activates the cold-sensitive TRPM8 receptors in the skin. Menthol, after topical application, causes a feeling of coolness due to stimulation of 'cold' receptors by inhibiting Ca++ currents of neuronal membranes. It may also yield analgesic properties via kappa-opioid receptor agonism.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

S. No.	Ingredients	Specification
1	Sucrose	BP
2	Glycerine	BP
3	Propylene Glycol	BP
4	Sodium Benzoate	BP
5	Bronopol	BP
6	Di Sodium EDTA	BP
7	Sodium Citrate	BP
8	Tartazine Yellow Supra	IH
9	Sweet orange Flavour 618	IH
10	Mixed Fruit Flavour 1038	IH
11	Pine Apple Flavour No .1	IH
12	Bittermask Flavour No .1	IH
13	Purified Water	BP

6.2 Incompatibilities

Not Known.

6.3 Shelf life

24 month

6.4 Special precautions for storage

Store below 30°C. Protect from light.

Keep out of reach of Children

6.5 Nature and contents of container

a) **Type of package**

100ml Amber coloured glass bottle.

b) **Nature and packaging material**

100ml Amber coloured glass bottle with ROPP cap and Measuring Cup packed in a laminated carton with Pack Insert

6.6 Special Precautions for disposal and other handling

Dispose the bottle carefully after use.

7. Marketing Authorisation Holder and Manufacturing site addresses

Marketing Authorisation Holder:

Prisma Pharma FZE
P.O. Box 17269
Jebel Ali Free Zone
Dubai, U.A.E.
Tel: +971 48816016 Fax: +971 48816056

Manufacturing Site:

THE MADRAS PHARMACEUTICALS

No. 137-B Old Mahabalipuram Road,

Karapakkam, Chennai -600 096, India

Tel: +91 44 2345 2040-44 Fax: +91 44 2345 2046

8. Marketing Authorization Number - Nil

9. Date of First Registration/Renewal of the Registration – New Registration

10. Date of Revision of the text –Nil

11. Dosimetry (If Applicable) – Not Applicable

12.Instructions for preparation of Radiopharmaceuticals (If Applicable) – Not Applicable