1.5 Product Information

1.5.1 Prescribing information (Summary of Product Characteristics)

1. NAME OF THE MEDICINAL PRODUCT

PHAMACOFF-P (Dextromethorphan Hydrobromide Syrup 5mg/5ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:

Dextromethorphan Hydrobromide BP	5 mg
Flavoured syrup base	q. s.
Colour: Ponceau 4R Supra	

Sr. No.	Raw materials	Pharmacopoeia	Function
1.	Sucrose	BP	Sweetening agent
2.	Methyl Hydroxybenzoate	BP	Preservative
3.	Propyl Hydroxybenzoate	BP	Preservative
4.	Sodium Benzoate	BP	Preservative
5.	Propylene Glycol	BP	Solvent
6.	Liquid Sorbitol (Non-Crystallizing)	BP	Sweetening agent

Safety Concern Information for Excipients

Excipients	Information of package leaflet	comments	Reference Each 5 ml in mg	Maximum Potency Per unit Dose (mg/5ml)	Maximum Daily Exposure (MDE)
Sucrose	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take	2000.00	----	70000mg

Sorbitol	This medicine contains x mg sorbitol in each <dosage unit><unit volume> <which is equivalent to x mg/ <weight><volume>>.	The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products	500.00	4370mg/ 5ml	
Propylene Glycol	If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.	While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or	1000.00	-------	5700 mg
Methyl Hydroxybenzoate	May cause allergic reactions (possibly		7.500	-------	60 mg
Sodium Benzoate	May cause allergic reactions (possibly		1.500	--------	60 mg
Propyl Hydroxybenzoate	May cause allergic reactions (possibly		1.500	-------	

3. PHARMACEUTICAL FORM

Oral Syrup

A reddish coloured, flavoured syrup.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PHAMACOFF-P (Dextromethorphan Hydrobromide Syrup 5mg/5ml) is indicated as an antitussive, for the relief of an unproductive cough.

4.2 Posology and method of administration Adults and

Children aged 12 years and over: Posology

10 ml syrup 4 times a day.

Maximum daily dose: 60mg Dextromethorphan

Children under 12 years:

This product is contraindicated in children under the age of 12 years

The Elderly (over 65 years) As for

adults above. Hepatic/renal

dysfunction

Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of moderate to severe hepatic impairment (see Pharmacokinetics).

Do not exceed the stated dose.

Keep out of the sight and reach of children.

Method of Administration

For oral use

4.3 Contraindications

PHAMACOFF-P is contraindicated in individuals with known hypersensitivity to the active substance or to any of the excipients.

PHAMACOFF-P is contraindicated in individuals who are taking, or have taken, monoamine oxidase inhibitors within the preceding two weeks.

Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to subjects in, or at risk of developing respiratory failure.

This product is contraindicated in patients taking serotonin reuptake inhibitors
Not to be used in children under the age of 12 years.

4.4 Special warnings and special precautions for use

PHAMACOFF-P 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.

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.

Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

This product should not be taken with any other cough and cold medicine.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

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 metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

This product should be used with caution in atopic children due to histamine release.

Patients with rare hereditary problems of fructose intolerance, glucose- galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains 500mg sorbitol per 5ml dose. Sorbitol may cause gastrointestinal discomfort and mild laxative effect. Patients with rare hereditary problems of fructose intolerance should not take this medicine because this product contains Sorbitol

4.5 Interaction with other medicinal products and other forms of Interaction

Dextromethorphan should not be used concurrently in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping
treatment with MAOIs as there is a risk of serotonin syndrome (e.g. hyperpyrexia, hallucinations, gross excitation or coma).

CYP2D6 inhibitors

Dextromethorphan is metabolized 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 fluoxetine, 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.

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics and other CNS depressant drugs.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Dextromethorphan should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risk to the developing foetus or nursing infant.

It is not known whether dextromethorphan or its metabolites are excreted in breast milk.

4.7 Effects on ability to drive and use machines

Unlikely to produce an effect.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When taking this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
- The medicine has been taken to treat a medical or dental problem and
- You have taken it according to the information provided with the Medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

Adverse effects are rare, however the following side effects may be associated with dextromethorphan hydrobromide: Gastrointestinal Disorders

Rare: Gastrointestinal upset

Nervous System Disorders

Rare: Dizziness, drowsiness, mental confusion

Immune System Disorders

Hypersensitivity

Psychiatric disorders:

Frequency unknown: Drug dependence (see section 4.4) General disorders and administration site conditions: Frequency unknown: drug withdrawal syndrome

4.9 Overdose

<u>Signs and symptoms</u>

Dextromethorphan is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms of overdose may include: mydriasis, nausea and vomiting, CNS depression, excitation, lethargy, nystagmus, psychomotor hyperactivity, serotonin syndrome, somnolence (drowsiness), dizziness, dysarthria (slurred speech), mental confusion, psychotic disorder (psychosis), and respiratory depression.

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 (0.01mg/kg body weight).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough Suppressant, Opium alkaloids and derivatives

ATC code no. R05DA09

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.

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. The onset of antitussive effects are 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.

5.2 Pharmacokinetic properties

Pharmacokinetics:

Absorption

Dextromethorphan is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in approximately 2 to 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 to 6 hours after ingestion of dextromethorphan.

Distribution

Dextromethorphan is widely distributed in the human body.
Dextromethorphan and its active metabolite, dextrorphan, are actively 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 kidney 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; dextrorphan is between 3.4 to 5.6 hours. The half-life of dextromethorphan in poor metabolisers is extremely prolonged, in the Range of 45 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Raw materials	Pharmacopoeia
1.	Sucrose	BP
2.	Methyl Hydroxybenzoate	BP
3.	Propyl Hydroxybenzoate	BP
4.	Disodium Edetate	BP
5.	Sodium Benzoate	BP
6.	Sodium Saccharine	BP
7.	Colour Ponceau-4R-supra	IHS
8.	Propylene glycol	BP
9.	Liquid Sorbitol (Non-Crystallizing)	BP
10.	Essence Raspberry	IHS
11.	Purified Water	BP

6.2 Incompatibilities

None known.

6.3 Shelf life

36 Months

Shelf life after first opening:

6 month after opening the cap of bottle.

6.4 Special precautions for storage

Store below 30ºC in dry and dark place. Do not freeze.

6.5 Nature and contents of container

Plastic (PET) round bottle 60 ml, Aluminum P.P Caps 25mm & Measuring Cups 25 mm are used as primary packaging material for packing the **PHAMACOFF-P** (Dextromethorphan Hydrobromide Syrup 5mg/5ml). 60 ml Plastic (PET) round bottle, Aluminum P.P Caps 25mm & Measuring Cups 25 mm are packed in an overprinted carton along with Leaflet (1 x 60ml). Such 100 bottles (100 x 1 x 60 ml) are packed in a 5 ply corrugated shipper box.

6.6 Instructions for use and handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
Aurochem Laboratories (India) Pvt. Ltd.
333, Gundecha Industrial Complex,
3rd Floor, Akurli Road, Kandivali – (East),
Mumbai – 400 101. INDIA
Email: info@aurochempharma.com
Phone: +(91)-(22)- 4250 9191
Fax: +(91)-(22)- 4250 9150 website:
www.aurochem.global

8. Marketing Authorization Number (S)

TAN 22 HM 0344

9. Date of First Authorization /Renewal of the Authorization

21/09/2022

10. Date of Revision of the Text
