For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

PIRITON CS

1. GENERIC NAME

Chlorpheniramine Maleate with Dextromethorphan Hydrobromide Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml (one teaspoonful) contains:

Chlorpheniramine Maleate IP	4 mg
Dextromethorphan Hydrobromide IP	10 mg

Colour: Carmoisine
in a flavoured syrup base containing Menthol IP

3. DOSAGE FORM AND STRENGTH

Syrup

Each 5 ml (one teaspoonful) contains:

Chlorpheniramine Maleate IP	4 mg
Dextromethorphan Hydrobromide IP	10 mg

Colour: Carmoisine
in a flavoured syrup base containing Menthol IP

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

PIRITON CS is indicated for the temporary relief of cough due to throat irritation, sneezing and running nose.

4.2 Posology and Method of Administration

For oral administration only.

Do not exceed the stated dose or frequency of dosing.

Should not be used with other cough and cold medicines.

Reassess patient, if symptoms persist more than 7 days.

Minimum dosing interval: 4 hours

Adults and Children aged 12 years and over

5 ml 4 hourly

Maximum daily dose 30 ml in any 24 hours.

Children (6-12 years)

2.5 ml 4 hourly

Maximum daily dose 15 ml in any 24 hours.

Children (2-6 years)

1.25 ml 4 hourly

Maximum daily dose 7.5 ml in any 24 hours.

PIRITON CS should not be used in children aged less than 2 years.

Special Populations

Elderly

5 ml 4 to 6 hourly

Maximum daily dose is 15 ml in any 24 hours.

Renal Impairment

Caution should be exercised while using in a patient with severe renal impairment defined as a Glomerular Filtration Rate (GFR) <30 mL/min/1.73m^2 (See 4.4 *Special Warnings and Precautions for Use*).

Hepatic Impairment

Caution should be exercised while using in a patient with severe hepatic impairment defined as bilirubin >50 micromol/l and albumin <28 g/l. (See 4.4 *Special Warnings and Precautions for Use*).

4.3 Contraindications

PIRITON CS is contraindicated in patients:

- With a prior severe hypersensitivity reaction to dextromethorphan or history of hypersensitivity to chlorpheniramine maleate or any other ingredients of the preparations (see *List of Excipients, 4.8 Undesirable Effects*).
- With, or at risk of developing, respiratory failure (e.g. those with chronic obstructive airways disease or pneumonia, or during an asthma attack or an exacerbation of asthma).
- Who are being treated or have been treated with monoamine oxidase inhibitors (MAOIs) within the previous fourteen days. Anticholinergic properties of chlorpheniramine are intensified by MAOIs.

4.4 Special Warnings and Precautions for Use

Caution should be exercised before administering *PIRITON CS* to individuals with the following:

- Chronic or persistent cough, such as occurs with asthma and emphysema, chronic bronchitis or where cough is accompanied by excessive secretions.
- Severe hepatic impairment.
- Severe renal impairment.
- Concomitant use of a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant (see 4.5 *Drug Interactions*).

Dextromethorphan is metabolised 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 4.5 *Drug Interactions)*.

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.

Patient should be reassessed if the cough persists for more than 7 days, or if it is accompanied by high fever, skin rash or persistent headache.

PIRITON CS should not be used with other cough and cold medicines and other anti-histamine containing products.

Chlorpheniramine may increase the effects of alcohol. Concomitant use of alcohol with *PIRITON CS* should be avoided.

Concurrent use with drugs which cause sedation such as anxiolytics and hypnotics may cause an increase in sedative effects; therefore, caution should be exercised before administering *PIRITON CS* concurrently with these medicines.

PIRITON CS, due to its chlorpheniramine content which has anticholinergic effects, should be used with caution in epilepsy, severe hypertension and cardiovascular disease, raised intra-ocular pressure including glaucoma, prostatic hypertrophy, bronchitis, bronchiectasis and bronchial asthma.

The anticholinergic properties of chlorpheniramine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.

Children and the elderly are more likely to experience neurological anticholinergic effects and paradoxical excitation of chlorpheniramine (e.g. increased energy, restlessness, nervousness).

Avoid use in elderly patients with confusion

Maximum recommended dose or frequency of dosing should not be exceeded.

PIRITON CS contains sucrose. This should be taken into account in the case of diabetes or low-calorie diets. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take *PIRITON CS*.

PIRITON CS contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Keep out of sight and reach of children.

4.5 Drug Interactions

Chlorpheniramine Maleate

Concurrent use of chlorpheniramine and hypnotics or anxiolytics may potentiate drowsiness. Concurrent use of alcohol may have a similar effect. (See 4.4 *Special Warnings and Precautions for Use).*

Chlorpheniramine inhibits phenytoin metabolism and can lead to phenytoin toxicity.

The anticholinergic effects of chlorpheniramine are intensified by MAOIs (see 4.3 *Contraindications*).

Dextromethorphan

The use of dextromethorphan with, or within two weeks of taking monoamine oxidase inhibitors (MAOIs) should be avoided as severe reactions including serotonin syndrome have been reported with dextromethorphan (see 4.3 *Contraindications*).

Caution should be exercised before taking dextromethorphan in combination with the following drugs:

- Concomitant use of dextromethorphan with selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants may result in serotonin syndrome with changes in mental status, hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor (see 4.4 *Special Warnings and Precautions for Use*).
- Dextromethorphan is metabolized by cytochrome P450 2D6 (CYP2D6) and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the serum levels dextromethorphan in the body. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Drugs which inhibit CYP2D6 include the antiarrhythmics quinidine and amiodarone, antidepressants such as fluoxetine and paroxetine, or other drugs which inhibit CYP2D6 such as haloperidol and thioridazine. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.
- Concomitant use of dextromethorphan and alcohol may increase the CNS depressant effects of both drugs.

4.6 Use in Special Populations

Fertility

There are no relevant clinical data available regarding effects on fertility from patients taking dextromethorphan.

The results of non-clinical studies have demonstrated a lack of adverse effects on fertility following oral administration of dextromethorphan to rats and rabbits (See *6 Nonclinical Properties*).

No relevant data available for chlorpheniramine.

Pregnancy

There are no adequate data from the use of chlorpheniramine maleate in pregnant women. The potential risk for humans is unknown.

There are no relevant clinical data available regarding effects on pregnancy from patients taking dextromethorphan.

The results of non-clinical studies have demonstrated a lack of adverse effects on fetal development and postnatal viability following oral administration of dextromethorphan to rats and rabbits during pregnancy (See 6 *Nonclinical Properties*)

PIRITON CS should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the foetus.

Lactation

Chlorpheniramine maleate may inhibit lactation and may be secreted in breast milk. There are no relevant clinical or non-clinical data available regarding effects on lactation from patients taking dextromethorphan.

PIRITON CS should not be used during lactation unless the benefit to the mother outweighs the potential risk to the new born.

4.7 Effects on Ability to Drive and Use Machines

The anticholinergic properties of chlorpheniramine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery (see 4.4 *Special Warnings and Precautions for Use).*

Patients should not drive or operate machinery if affected by drowsiness or dizziness.

4.8 Undesirable Effects

In absence of availability of adverse event data on the fixed dose combination of dextromethorphan and chlorpheniramine, adverse event data of the individual ingredients is presented below.

Chlorpheniramine Maleate

The following convention has been utilised for the classification of the frequency of adverse reactions: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse reactions identified during post-marketing use with chlorphenamine are listed below. As these reactions are reported voluntarily from a population of uncertain size, the frequency of some reactions is unknown but likely to be rare or very rare:

System organ class	**Adverse Reaction**	**Frequency**
Nervous system disorders*	Sedation, somnolence	Very common
	Disturbance in attention, abnormal coordination, dizziness, headache	Common
Eye disorders	Blurred vision	Common
Gastrointestinal disorders	Nausea, dry mouth	Common
	Vomiting, abdominal pain, diarrhoea, dyspepsia	Unknown
General disorders and administration site conditions	Fatigue	Common
	Chest tightness	Unknown
Immune system disorders	Allergic reactions, angioedema, anaphylactic reactions	Unknown
Metabolism and nutritional disorders	Anorexia	Unknown
Musculoskeletal and connective tissue disorders	Muscle twitching, muscle weakness	Unknown
Psychiatric disorders*	Confusion, excitation, irritability, nightmares, paradoxical excitation (increased energy, restlessness, nervousness)	Unknown
Renal and urinary disorders:	Urinary retention	Unknown
Skin and subcutaneous disorders	Exfoliative dermatitis, rash, urticaria, photosensitivity	Unknown
Respiratory, thoracic and mediastinal disorders	Thickening of bronchial secretions	Unknown
Vascular disorders	Hypotension	Unknown

**Children and the elderly are more susceptible to neurological anticholinergic effects and paradoxical excitation.*

Dextromethorphan

The following adverse events have been observed in clinical trials with dextromethorphan and are likely to represent uncommon adverse reactions to dextromethorphan (i.e. occurring in ≥1/1,000 to <1/100 patients). Adverse reactions are listed below by MedDRA System Organ Class.

Body System	Undesirable effect
Nervous system disorders	Drowsiness, dizziness
Gastrointestinal disorders	Gastrointestinal disturbance, nausea, vomiting, abdominal discomfort

Post Marketing Data (Dextromethorphan)

Adverse reactions identified during post-marketing use are listed below. As these reactions are reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown but likely to be rare or very rare (occurring in < 1/1000 patients).

Body System	Undesirable effect
Nervous system disorders	Serotonin syndrome (with changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor and hypertension) has been reported when dextromethorphan has been taken concurrently with MAOIs or serotonergic drugs such as SSRIs (see 4.3 *Contraindications and* 4.5 *Drug Interactions*).
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria, angioedema)

4.9 Overdose

Symptoms and Signs

Chlorpheniramine overdose is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include toxic psychosis, convulsions, apnoea, dystonic reactions and cardiovascular collapse including arrhythmias.

Dextromethorphan overdose is likely to result in effects similar to those listed under *Undesirable Effects*. Following large overdoses, additional symptoms may include excitation, mental confusion, restlessness, nervousness and irritability, stupor, ataxia, dystonia, hallucinations, psychosis and respiratory depression.

Treatment

Management should be as clinically indicated.

Supportive and symptomatic care should be provided as required. If overdose is severe, naloxone may be helpful, particularly for patients with respiratory depression.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Chlorpheniramine Maleate

Chlorpheniramine maleate is an antihistamine inverse agonist of H1- receptor.

Chlorpheniramine also has anticholinergic activity.

Dextromethorphan

Dextromethorphan has an antitussive action. It controls cough spasms by depressing the medullary cough centre. It is also an antagonist of N-methyl-d-aspartate (NMDA) receptors and a σ-receptor agonist.

5.2 Pharmacodynamic Properties

Chlorpheniramine Maleate

Pharmacotherapeutic group: Antihistamines for systemic use; ATC code: R06AB04.

Antihistamines act to decrease antigen presentation, mediator release and diminish expression of pro-inflammatory cytokines, cell adhesion molecules and chemotactic factors. The actions of chlorpheniramine include inhibition of histamine on smooth muscle, capillary permeability and hence reduction of oedema and wheal in hypersensitivity reactions such as allergy.

Duration of action of 3 to 6 hours has been reported with significant intersubject variation in reported duration of action.

Dextromethorphan

Pharmacotherapeutic group: Cough suppressants (opium alkaloids and derivatives); ATC Code: R05DA09.

Dextromethorphan is a cough suppressant which has a central action on the cough centre of the medulla.

5.3 Pharmacokinetic Properties

Absorption

Chlorpheniramine Maleate

The peak plasma concentrations occurs about from 2.5 to 6 hours after administration. The bioavailability is low: values of 25 to 50% have been reported.

Dextromethorphan

Dextromethorphan hydrobromide is well absorbed from the gastrointestinal tract.

Distribution

Chlorpheniramine Maleate

Approximately 70% of chlorphenamine in the circulation is bound to plasma proteins. It is distributed in the body, including the CNS. Extensive uptake by lungs, kidneys, liver, and brain have been shown. Volume of distribution of 7.0 L/kg has been reported after oral dosing.

Dextromethorphan

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

Metabolism

Chlorpheniramine Maleate

Chlorphenamine undergoes considerable first-pass metabolism. Chlorphenamine is extensively metabolized via demethylation in the liver, forming desmethyl - and didesmethylchlorphenamine.

Dextromethorphan

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.

Elimination

Chlorpheniramine Maleate

The half-life varies from 2 to 43 hours. Unchanged drug and metabolites are excreted mainly in urine. Considerable intersubject variation (two- to fivefold differences in urinary metabolite excretion) in chlorpheniramine metabolism is found.

Dextromethorphan

Dextromethorphan and its metabolites are excreted in urine for up to 50% of the ingested dose at 24 hours. Only a very small quantity of unchanged dextromethorphan is found in the urine.

The elimination half-lives of dextromethorphan vary greatly depending on the dose administered and on the patient's CYP2D6 phenotype.

In one study, the half-life of the elimination phase of dextromethorphan was on average approximately 7 times higher in some subjects. The half-life of main metabolite dextrorphan is 2.5-3.5 hours.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology and Pharmacology

Non-Clinical safety data on chlorpheniramine maleate and dextromethorphan obtained from the literature or in house have not revealed findings which are of relevance to the recommended dosage and use of the product.

Dextromethorphan

Reproductive and Developmental Toxicology

The results of non-clinical studies have demonstrated a lack of adverse effects on fertility, fetal development and postnatal viability following oral administration of up to 50 mg/kg/day of dextromethorphan to rats (estimated to be approximately 4 times the daily maximum human equivalent therapeutic dose of 120 mg/day) and rabbits (estimated to be approximately 8 times the daily maximum human equivalent therapeutic dose of 120 mg/day) during pregnancy during pregnancy.

7. DESCRIPTION

Syrup

Each 5 ml (one teaspoonful) contains:

Chlorpheniramine Maleate IP	4 mg
Dextromethorphan Hydrobromide IP	10 mg

Colour: Carmoisine
in a flavoured syrup base containing Menthol IP

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Sucrose, Sodium Benzoate, Sodium Chloride, Citric Acid Monohydrate, Sodium Citrate, Saccharin Sodium, Glycerin, Sorbitol Solution, Propylene Glycol, Colour Carmoisine, Flavour Strawberry, Flavour Raspberry, Flavour peppermint, Menthol, Purified Water.

8.1 Incompatibilities

No incompatibilities have been identified

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Bottle with a measure cup.

8.4 Storage and Handling Information

Store in a well closed container at temperatures not exceeding 30^{o}C, protected from direct sunlight.

Keep out of reach of children.

For oral use only.

It is dangerous to take this preparation except under medical supervision

There are no other special requirements for use and handling of this product

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients and/or their patients' parents about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *PIRITON CS*. Patients may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging

12. DATE OF REVISION

15-NOV-19

Trade marks are owned by or licensed to the GSK group of companies.

Version No: PIRCS/PI/IN/2019/01.

Adapted from:

1. *Chlorpheniramine Maleate GDS Version Number 3 dated 19 February 2019*
2. *Dextromethorphan GDS Version Number 4 dated 20 July 2017*
3. *Clinical Pharmacology - Dextromethorphan Monograph available from: https://www.clinicalkey.com/pharmacology/monograph/179?sec=monindi Revision date 22 May 2017 Accessed on 11 November 2019*
4. *Martindale; The Complete Drug Reference:*
    a. *Chlorpheniramine Maleate: https://www.medicinescomplete.com/#/content/martindale/6116-v?hspl=Chlorpheniramine. Latest modified on 31July 2019, accessed on 8 Nov 2019.*

b. *Dextromethorphan:*
https://www.medicinescomplete.com/#/content/martindale/5634-t#content%2Fmartindale%2F5634-t%235634-t
Latest modified on 31July 2019, accessed on 8 Nov 2019.