1.4 Product information

1.4.1 Prescribing information (Summary of Product Characteristics)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT:

Paracetamol BP + Phenylephrine Hydrochloride BP + Chlorphenamine Maleate BP + Caffeine BP Tablets **(COLDAREST TABLETS)**

1.1 Strength:

Each uncoated Tablet Contains:

Paracetamol BP……....500 mg

Phenylephrine Hydrochloride BP ……..5 mg

Chlorphneiramine Maleate BP…….….. 2 mg

Caffeine (Anhydrous) BP…….…….30 mg

1.2 Pharmaceutical form:

Oral Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 Qualitative Declaration:

Sr. No.	Name of Raw Materials	Specification or reference text
1	Paracetamol	BP
2	Phenylephrine hydrochloride	BP
3	Chlorphenamine maleate	BP
4	Caffeine (anhydrous)	BP
5	Microcrystalline cellulose (Ran-Q)102	BP
6	Starch (Maize)	BP
7	Colloidal anhydrous silica	BP
8	Pregelatinised starch	USP/NF
9	Methyl paraben	BP
10	Polyvinyl Pyrrolidone K – 30 (Povidone K-30)	BP
11	Polyethylene glycol 6000	USP/NF
12	Purified water	BP
13	Sodium starch glycollate	BP
14	Croscarmellose sodium	USP/NF
15	Crospovidone	USP/NF
16	Talc	USP
17	Magnesium stearate	BP

2.2 Quantitative Declaration

Standard Batch Size: 10,00,000 tablets

Sr. No.	Name of Raw Materials	Overages	Qty./Tablet (in mg)	Standard batch quantity (in Kg)	Specification or reference text
I. DRY MIXING (2, 50, 000 Tablets)					
1	Paracetamol	-	500.00	125.000	BP
2	Phenylephrine hydrochloride	2.5%	5.00	1.281	BP
3	Chlorphenamine maleate	2.5%	2.00	0.513	BP
4	Caffeine (anhydrous)	-	30.00	7.500	BP
5	Microcrystalline cellulose (Ran-Q)102	-	14.70	3.675	BP
6	Starch (Maize)	-	17.00	4.250	BP
7	Colloidal anhydrous silica	-	2.252	0.563	BP
8	Pregelatinised starch	-	5.000	1.250	USP/NF
II. BINDER (2, 50, 000 Tablets)					
1	Starch BP	-	24.500	6.125	BP
2	Methyl paraben	-	1.00	0.250	BP
3	Polyvinyl Pyrrolidone K – 30 (Povidone K-30)	-	8.00	2.000	BP
4	Polyethylene glycol 6000	-	2.50	0.625	USP/NF
5	Purified water	-	Q.S.	27.000 Lts	BP
III.LUBRICATION (10,00,000 Tablets)					
1	Colloidal anhydrous silica	-	3.748	3.748	BP
2	Sodium starch glycollate	-	6.500	6.500	BP
3	Croscarmellose sodium	-	7.500	7.500	USP/NF
4	Crospovidone	-	2.500	2.500	USP/NF
5	Talc	-	4.000	4.000	USP
6	Magnesium stearate	-	6.000	6.000	BP
7	Microcrystalline cellulose (Ran-Q)102	-	10.500	10.500	BP

3. PHARMACEUTICAL FORM:

White, round flat bevelled uncoated tablets with a breakline on one side and 'CENTAUR' embossed on the other side

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

COLDAREST is indicated for:

- Relief of nasal and sinus congestion.
- Relief of allergic symptoms of the nose or throat due to upper respiratory tract allergies.
- Relief of sinus pain and headache.
- Adjunct with anti-bacterials in sinusitis, tonsillitis and otitis media.
- Post-operative after tonsillectomy.

4.2 Posology:

- Adults: 1 tablet 3 – 4 times daily.
- Children (6 – 12 years): ½ tablet 3 – 4 times daily.
- Children (2 – 6 years): ¼ tablet 3 – 4 times daily

4.3 Method of administration: As directed by the physician.

4.4 Contraindications:

COLDAREST is contraindicated in patients hypersensitive to any component of the drug and in those patients on concurrent MAO inhibitor therapy. Patients known to be hypersensitive to other antihistamines or sympathomimetic amines may exhibit cross sensitivity with Coldarest. Phenylephrine in COLDAREST, is contraindicated in patients with heart disease, hypertension, diabetes or hyperthyroidism.

4.5 Special warnings and precautions for use:

Warnings

Phenylephrine:

Hypertensive crises can occur with concurrent use of phenylephrine and monoamine oxidase (MAO) inhibitors, indomethacin or with beta-blockers and methyldopa. If a hypertensive crisis occurs these drugs should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Fever should be managed by means of external cooling.

Chlorphenamine:

Antihistamines may produce drowsiness or excitation, particularly in children and elderly patients.

Precautions:

Antihistamines such as Chlorphenamine maleate, may impair the mental and /or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; phenylephrine may product a rapid pulse, dizziness or palpitations; patients should be cautioned accordingly.

In case a hypersensitivity reaction occurs which is rare, COLDAREST should be discontinued.

COLDAREST contains paracetamol therefore should not be used in conjunction with other paracetamol containing products.

COLDAREST should be used with caution in patients with renal or hepatic dysfunction, diabetes mellitus, hyperthyroidism, cardiovascular problems, epilepsy and closed angle glaucoma.

4.6 Pediatric population

None.

4.7 Interaction with other medicinal products and other forms of interaction:

The use of Phenylephrine with other sympathomimetic a mines and MAO inhibitors may produce an additive elevation of blood pressure. MAO inhibitors may prolong the anticolinergic effect of antihistamine.

Clinically significant drug interactions may occur on concomitant administration of COLDAREST with monoamine oxidase inhibitors, tricyclic antidepressants, B-adrenergic agents, methyldopa and reserpine.

4.8 Additional information on special populations: None

4.9 Pediatric population: None.

4.10 Fertility, Pregnancy and lactation:

4.10.1 General principles

4.10.2 Woman of childbearing potential / Contraception in males and females.

4.10.3 Pregnancy

4.10.4 Breastfeeding

4.10.5 Fertility

Coldarest Tablet is use with precautions in pregnant women and in nursing mothers.

4.11 Effects on ability to drive and use machines:

No adverse effects known.

4.12 Undesirable effects:

COLDAREST is generally well tolerated and adverse events are rare. Hypersensitive individuals may display ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness. and Nausea. Use of sympathominetics has been associated with fear, anxiety, restlessness, tremor, weakness, dysuria, insomnia, hallucinations and convulsions. Chlorphenamine in COLDAREST may cause sedation.

4.13 Overdose:

Hypersensitive individuals may display ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness and nausea. Use of sympathominetics has been associated with fear, anxiety, restlessness, tremor, weakness, dysuria, insomnia, hallucinations and convulsions. Chlorphenamine Maleate in COLDAREST TABLETS may cause sedation.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

COLDAREST Tablets contains clinically proven analgesic-antipyretic paracetamol with decongestant Phenylephrine and an antihistamine Chlorphenamine Paracetamol produces analgesia by elevation of the pain threshold and antipyretic effect through action on the hypothalamic heat-regulating center. Paracetamol is equal to aspirin in analgesic and antipyretic effectiveness, and it is unlikely to produce many of the side effects associated with aspirin containing products.

Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the. half -life in plasma is about 2 hours after therapeutic doses. Acetaaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma protein is variable; only 20% to 50% may be bound at the concentration encountered during acute intoxication. After therapeutic doses, 90% to 100% (If the drug may be recovered in the urine within the first day, primarly after hepatic conjugation. With glucuronic acid (about 60%), sulphuric acid (about 35%, or cysteine (about 3%); small amount of hydroxylated and deacetylated metabolites also have been detected; Children have less capacity for glucuronidation of the drug than do adults. A small proportion of acetaminophen undergoes cytochrome P450 - mediated N - hydroxylation to form N - acetyl - benzoquinoneimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl group in glutathione. However, after ingestion of large doses or acetaminophen, the metabolite is formed in amounts

sufficient to deplete hepatic glutathione, Under these circumstances, reaction with sulfhydryl groups in hepatic protein is increased and hepatic necrosis can result, perhaps in part as a result of intracellular accumulation of Ca 2^{+} dependent endonuclease, And resultant DNA fragmentation. Chlorphenamine in Coldarest Tablets provides prompt relief of itchy watery eyes, runny nose, sneezing, itching of the nose or throat due to respiratory allergies. The HI antagonists are well absorhed from the gastrointestinal tract; following oral administration, peak plasma, concentrations are achieved in 2 to 3 hours and effects usually last 4 to 6 hours; however, some of the drugs are much longer acting. Extensive studies of the metabolic fate of the older H1 antagonists are limited. Diphenhydramine, given orally, reaches a maximal concentration in the blood in about 2 hours, remains at about this level for another 2 hours, and then falls exponentially with. plasma elimination half time of about 4hours. The drug is widely distributed throughout the body, including the CNS. Little, if any is excreted unchanged in the urine; most appears there as metabolites. Other first generation H1antagonists appear to be eliminated in much the same way (see reviews by Witiak and Lewis, 1978; Paton and Webster,1985).

Information on the concentrations of these drugs achieved in the skin and mucous membranes is lacking. However, significant inhibition of "wheal – and – flare " responses to the intradermal injection of histamine or allergen may persist for 36 hours or more after treatment with some longer - Acting HI antagonists, even when concentrations of the drugs in plasma are very low. Such results emphasize the need for flexibility in the interpretation of the recommended dosage schedules less frequent dosage may suffice. Like many other drugs that are metabolized extensively, HI antagonists are eliminated more rapidly by children than by adults and more slowly in those with severe liver disese. HI -recepter antagonists are among the many drugs that induce hepatic microsomal enzymes, and they may facilitate their own metabolism (see Paton and Wehster, I985; Simons and Simons, 1988). The. second -generation HI antagonists astemizole, loratadine and. terfanadine are rapidly absorbed from the gastrointestinal tract and metabolised in the liver to active metehelities by hepatic microsomal. P450 system (Simons and Simons, 1994), Consequently, metabolism of these drugs can be affected by competition for the P450 enzymes by other drugs. This alteration of metabolism Can be

clinically significant (see "PolymorphicVentricular Tachycardia," below). Cetirizine, an active metabolite of hydroxyzine, and acrivastine also are well absorbed but primarily are excreted renally in the unmetabolized from (Brogden and Me Tavish,1991;Spencer et al., 1993; Barnes et al, 1993). COLDAREST TABLETS contains, in addition to the above ingredients, a decongestant, Phenylephrine, which is a sympathomimetic amine. It provides prompt relief of nasal and sinus congestion, Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscular it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about one hour and up to about two hours respectively. Intravenous injections are effective for about 20 minutes. Adverse effects have been observed as a result of systemic absorption from topical administration. Caffeine in Coldarest Tablet. enhances the, analgesic activity of' paracetamol and serves to reduce incidence of sedation due to Chlorphenamine. All the four drugs do not exhibit any interactions amongst themselves; in fact they supplement each other's action.

5.2 Pharmacokinetic properties:

Paracetamol:

Acetaminophen has analgesic and antipyretic effects that do not differ Significantly from those of aspirin. However, as mentioned, it has only weak anti-inflammatory effects. Minor metabolites contribute significantly to the toxic effects of acetaminophen. The pharmacological properties of acetaminophen have been reviewed by Clissold (1986). Exactly why acetaminophen is an effective analgesic -antipyretic but only a weak anti-inflammatory agent has not been satisfactorily explained. An anti-inflammatory effect can be demonstrated in animal models, but only at doses considerably in excess of' those required for analgesia. The failure of acetaminophen to exert anti-inflammatory activity may be attributed to the fact that acetaminophen is only a weak inhibitor of cyclooxygenase in the presence of the high concentrations of peroxide that are found in inflammatory lesions (Marshall et. al., 1987; Hanel and Lands, 1982). Further, acetaminophen does not Inhibit neutrophil activation, as do other NSAIDs (Abramson aud Weissmann, 1989). Single or repeated therapeutic does of

acetaminophen have no effects on the cardiovascular And respiratory system. Acids-base changes do not occur, nor does. The drug produces the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. Acetaminophen has no effect on platelets, bleeding time, or the excretion of uric acid. Paracetamol is an antipyretic and peripherally acting analgesic. Paracetamol produces analgesia by elevation of the pain threshold and antipyretic effect through action on the hypothalamic heat-regulating center. Paracetamol is equal to aspirin in analgesic and antipyretic effectiveness. It is however unlikely to produce many of the side effects associated with aspirin.

Phenylephrine hydrochloride

Phenylephrine Hydrochloride has its vasoconstrictor activity by releasing noradrenaline from sympathetic nerve endings, and by direct stimulation of (alpha) adrenoreceptors in blood vessels. Phenylephrine provides prompt relief of nasal and sinus congestion.

Chlorphenamine maleate

Chlorphenamine Maleate is competitive H1-receptor histamine. Blocking drug, thereby counteracting the effects of histamine release associated with allergic manifestations of upper respiratory tract inflammatory disorders. Hl-blocking drugs inhibit the actions of histamine on smooth muscle, capillary permeability, and can both stimulate and depress the central nervous system. Chlorphenamine in Coldarest provides prompt relief of itchy watery eyes, runny nose, sneezing, itching of the nose and throat due to respiratory allergies.

Caffeine

Caffeine is a central nervous system stimulant. Caffeine in Coldarest Tablets enhances the analgesic activity of Paracetamol and serves to reduce the sedation caused by Chlorphenamine.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included.

6.PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Sr. No.	Name of Raw Materials	Specification or reference text
1	Microcrystalline cellulose (Ran-Q)102	BP
2	Starch (Maize)	BP
3	Colloidal anhydrous silica	BP
4	Pregelatinised starch	USP/NF
5	Methyl paraben	BP
6	Polyvinyl Pyrrolidone K – 30 (Povidone K-30)	BP
7	Polyethylene glycol 6000	USP/NF
8	Purified water	BP
9	Sodium starch glycollate	BP
10	Croscarmellose sodium	USP/NF
11	Crospovidone	USP/NF
12	Talc	USP
13	Magnesium stearate	BP

6.2 Incompatibilities: None stated.

6.3 Shelf life: 36 months from the date of manufacture.

6.4 Special precautions for storage: Store at temperature between 15°C - 30°C in a dark place. Keep medicines out of reach of children.

6.5 Nature and contents of container:

Tablets of Coldarest Tablets are packed in one Blister pack and 10 such Blister packs are packed in one carton and 50 such cartons are packed in one corrugated box.

4 tablets are packed in one cover and 50 such catch covers are packed in a one carton and 18 such cartons are packed in one corrugated box.

6.6 Special precautions for disposal and other handling:

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS:

Marketing Authorization holder:

Registered office:

Centaur Pharmaceuticals Pvt. Ltd. Centaur House, Near Grand Hyatt, Shanti Nagar, Vakola, Santacruz (E), Mumbai 400 055, India

Manufacturing Site:

Centaur Pharmaceuticals Pvt. Ltd. Plant I, Plot No: 3, 5B, 2C, Tivim Industrial Estate, Karaswada, Mapusa Goa-403526

8. MARKETING AUTHORISATION NUMBER

Not applicable.

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10. DATE OF REVISION OF THE TEXT: AUGUST 2019

11. DOSIMETRY (IF APPLICABLE): NOT APPLICABLE.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

NOT APPLICABLE.