Triprolidine Hydrochloride & Codeine Phosphate Cough Syrup

COREX® T

1. GENERIC NAME

Triprolidine Hydrochloride & Codeine Phosphate Cough Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml (teaspoonful) contains:

Triprolidine Hydrochloride I.P.	1.25 mg
Codeine Phosphate I.P.	10 mg

List of excipients: Propylene Glycol I.P., Sorbitol (70%) I.P. Non Crystallising, Saccharin Sodium I.P. (as artificial sweetener), Sodium Citrate I.P., Glycerin I.P., Colors - Sunset Yellow FCF and Carmoisine, Flavour Pineapple PC, Menthol I.P., Nutmeg Oil, Methyl Paraben I.P., Propyl Paraben I.P., Purified Water I.P.

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Dosage : Syrup
Strength: Refer to Section 2

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Corex T syrup is indicated for symptomatic treatment of dry cough.

4.2 Posology and Method of Administration

Corex T syrup is usually given 1 teaspoonful (5 ml) orally 4 times a day in adults only.

4.3 Contraindications

Corex T is contraindicated in:

- Hypersensitivity to any of the ingredients
- Patients under the age of 18 years
- Women who are pregnant, or during labor and delivery
- Women who are breastfeeding

Patients who are known to be CYP2D6 extensive or ultra-rapid metabolizers for whom there is an increased risk of developing symptoms of opioid toxicity, even at commonly prescribed doses. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression which may be life-threatening and very rarely fatal.

Patients with lower respiratory tract symptoms, including asthma, bronchitis, bronchiectasis.

Patients with chronic or persistent cough, such as what occurs with asthma, smoking or emphysema, or where cough is accompanied by excessive secretions.

Patients in or at risk of developing respiratory failure.

Patients with severe hepatic impairment, as it may precipitate hepatic encephalopathy.

Patients with moderate to severe renal impairment (glomerular filtration rate less than 60 ml/min).

Patients with head injury or raised intracranial pressure, since further depression of respiration will increase cerebral edema.

Patients with ulcerative colitis, since in common with other opioid analgesics, codeine may precipitate toxic dilatation or spasm of the colon.

4.4 Special warnings and precautions for Use

General

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of the cough is identified, that modification of the cough does not increase the risk of clinical or physiological complications, and that appropriate therapy for the primary disease is provided.

Corex T should not be used in patients with a history of arrhythmia, epilepsy, increased intraocular pressure (narrow angle glaucoma), prostatic hypertrophy, bladder neck obstruction, diabetes mellitus, ischemic heart disease and hyperthyroidism, unless its benefits outweigh its risks in these patients.

Corex T should be prescribed with caution for certain special at risk patients such as the elderly and debilitated, for those with gallbladder disease or gallstones, history of bronchial asthma, or urethral stricture.

Although codeine may be habit forming when used over long periods or in high doses, studies indicate that addiction to codeine is uncommon and requires high parenteral doses. Nevertheless, patients should take the drug only for as long, in the amounts, and as frequently as prescribed.

Large doses of codeine may cause the release of significant quantities of histamine, which may be associated with hypotension, cutaneous vasodilation, urticaria and, more rarely, bronchoconstriction.

Corex T should not be used more than recommended by the physician.

Gastrointestinal

Corex T should not be used in patients with obstructive bowel disorder or acute abdominal conditions (i.e. acute appendicitis or pancreatitis), stenosing peptic ulcer or pyloroduodenal obstruction, unless its benefits outweigh its risks in these patients.

Codeine may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions

Respiratory

Codeine, including Corex T is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

Opioids can cause central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Ultra-rapid Metabolizers of Codeine

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Neurological Symptoms

There is a risk of drowsiness, malaise, tiredness, dizziness, 'spinning' sensation, fits, increased pressure in the skull (painful eyes, changes in vision or headache behind the eyes), headache, tolerance (medicine has less effect) or dependence (suffer from withdrawal symptoms e.g. tremor, sweating, increased heart rate, increased breathing rate, raised blood pressure and feeling or being sick if the medicine is stopped too quickly).

Serotonin Syndrome

Caution is advised when Corex T is co-administered with drugs that affect the serotonergic neurotransmitter systems. The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs (see section 4.5). This may occur within the recommended dose.

Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyper-reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). If serotonin syndrome is suspected, discontinuation of Corex T should be considered.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Androgen Deficiency

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Risks from concomitant use with benzodiazepines or other CNS depressants:

Concomitant use of opioids, including Corex T, with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of Corex T and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate (see section 4.5). Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Special Populations

Elderly

Although there have been no specific studies of Corex T in this group of patients, it may be anticipated that the elderly may be more susceptible to adverse effects. Therefore, reduced dosage and careful monitoring are advised, particularly in cases where there is impairment of renal, hepatic or mental status.
The elderly are more likely to experience neurological anticholinergic effects and paradoxical excitation.

Children
Corex T must not be used in patients under 18 years of age.
In young children, the respiratory centre is especially susceptible to the depressant action of opioid cough suppressants. Furthermore, some children may be ultra-rapid metabolisers of codeine.

Hepatic Insufficiency
Experience with the use of the product suggests that normal adult dosage is appropriate in the presence of mild to moderate hepatic impairment, although it may be prudent to exercise caution and reduce the dose.
There have been no specific studies of Corex T, in hepatic impairment.

Renal Insufficiency

Caution should be exercised when administering Corex T to patients with mild renal impairment, particularly if accompanied by cardiovascular disease.
There have been no specific studies of Corex T in renally impaired patients.

4.5 Drug Interaction

Corex T should not be used with other cough and cold medications with an antihistamine and antitussive.

Concomitant use of Corex T with tricyclic antidepressants, or with monoamine oxidase inhibitors.
This may increase the side effects of the Corex T.
Users of Corex T should avoid the concomitant use of alcohol or other centrally acting sedatives. Patients receiving other opioid analgesics, antipsychotics, tricyclic antidepressants, anxiolytics, hypnotics or other CNS depressants concomitantly with Corex T may exhibit increased sedation and an enhanced effect on respiratory inhibition.

Codeine, like other opioids, may antagonise the effects of metoclopramide and domperidone on gastrointestinal motility.

Co-administration of Corex T with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor (SSRI) or a Serotonin Norepinephrine Reuptake Inhibitor (SNRI), a tricyclic antidepressant (TCA), a triptan, a 5-HT3 receptor antagonist, a drug that affects the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Benzodiazepines and other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, and alcohol, increases the risk of respiratory depression, profound sedation, coma, and death (see section 4.4).

4.6 Use in Special population

Pregnancy
Corex T is contraindicated for use in pregnant women.

During the last trimester of pregnancy codeine may cause withdrawal symptoms in the neonate.

Administration of opioids during labour may produce gastric stasis and increase the risk of vomiting and aspiration pneumonia in the mother.

No clinical data on exposed pregnancies are available for Corex T. Animal studies with triprolidine do not indicate direct or indirect harmful effects on embryofetal development.

Lactation
Corex T is contraindicated in women who are breast-feeding. Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolisers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breast-fed infants. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breast-feeding, breathing difficulties, and decreased tone, in their baby. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.

Since there is a risk of infant exposure to codeine and morphine through breast milk, Corex T is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating paediatricians about any use of codeine during breast-feeding.

4.7 Effects on Ability to Drive and Use Machines

Corex T may cause drowsiness and impair performance in tests of auditory vigilance. There is individual variation in response to antihistamines.
Patients should be warned about engaging in activities requiring mental alertness such as driving a car, or operating dangerous machinery or hazardous appliances, until they are reasonably certain the Corex T does not adversely affect their performance.

4.8 Undesirable Effects

These may occur in occasional patients depending on his or her sensitivity to individual ingredients.

Triprolidine
Triprolidine may cause sedation, drowsiness, dizziness, disturbance in attention and abnormal coordination. Skin rashes, with or without irritation, have occasionally been reported. Dryness of the mouth, nose and throat may occur. Tachycardia, paradoxical excitation, confusion, nightmares, hallucinations, blurred vision, thickening of bronchial secretions, urinary retention, rash, urticaria and gastrointestinal disturbance including nausea and vomiting may also occur.

Codeine
In some patients, dizziness, worsening of headache with prolonged use, drowsiness, pruritus and sweating may occur.

In therapeutic doses, codeine is less likely than morphine to produce adverse effects. The most common adverse effects noted with codeine include nausea, vomiting and constipation. Micturition may be difficult. Dry mouth, vertigo, light-headedness,

tachycardia, rash and urticaria also occur. These effects occur more commonly in ambulant patients than those at rest in bed. Therapeutic doses of codeine occasionally induce hallucinations. Acute pancreatitis and symptoms of central nervous system depression may also occur. *Central sleep apnoea has been reported with opioid use as a class effect (see section 4.4)*.

Gastrointestinal:

Esophageal disorder: Cases of esophageal disorder (e.g., esophageal motility disorder, lower esophageal sphincter relaxation impaired, esophageal peristalsis decreased) have been reported with opioid therapy.

Endocrine Disorders:

Frequency not known: Adrenal insufficiency; Androgen deficiency.

4.9 Overdose

Overdosage with antihistamines with antimuscarinic activity such as triprolidine is associated with antimuscarinic, extrapyramidal, and CNS effects. In infants and children, CNS stimulation predominates over CNS depression. Excitation, confusion and respiratory depression may occur after overdosage with codeine. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment
Therapy, if instituted within 4 hours of overdosage, is aimed at reducing further absorption of the drug. In the conscious patient, vomiting should be induced even though it may have occurred spontaneously. If vomiting cannot be induced, gastric lavage is indicated. Adequate precautions must be taken to protect against aspiration, especially in children. Charcoal slurry or other suitable agents should be instilled into the stomach after vomiting or lavage. Saline cathartics or milk of magnesia may be of additional benefit.

In the unconscious patient, the airway should be secured with a cuffed endotracheal tube before attempting to evacuate the gastric contents. Intensive supportive and nursing care is indicated, as for any comatose patient. If breathing is significantly impaired, maintenance of an adequate airway and mechanical support of respiration is the most effective means of

providing adequate oxygenation. Hypotension is an early sign of impending cardiovascular collapse and should be treated vigorously.

Do not use CNS stimulants. Convulsion should be controlled by careful administration of diazepam or short-acting barbiturate, repeated as necessary. Physostigmine may be also considered for use in controlling centrally-mediated convulsions.

Ice packs and cooling sponge baths, not alcohol, can aid in reducing the fever commonly seen in children.

For codeine, continuous stimulation that arouses, but does not exhaust, the patient is useful in preventing coma. Continuous or intermittent oxygen therapy is usually indicated, while naloxone is useful as a codeine antidote. Close nursing care is essential.

Saline cathartics, such as milk of magnesia, help to dilute the concentration of the drugs in the bowel by draining water into the gut, thereby hastening drug elimination.

There are no specific antidotes to triprolidine. Histamine should not be given.

In severe cases of overdosage, it is essential to monitor both the heart by ECG and plasma electrolytes and to give I.V. potassium as indicated by these continuous controls. Vasopressors may be used to treat hypotension, and excessive CNS stimulation may be counteracted with parenteral diazepam. Stimulants should not be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Codeine: Opiates like codeine have a central mechanism of action on MORs in the medullary cough center, but there is some evidence that they may have additional peripheral action on cough receptors in the proximal airways. Triprolidine: Triprolidine is a potent, competitive histamine H1-receptor antagonist with antimuscaranic action.

5.2. Pharmacodynamic Properties

Codeine: Codeine and other centrally acting cough suppressants act directly on the cough centre in the brain and reduce the discharge of nerve impulses to the muscles that cause coughing. Codeine, by its action on the cough center in the brain, helps reduce excessive frequency and intensity of cough bouts, which allows the patient to rest or sleep.

Triprolidine: . Being an alkylamine, the drug possesses minimal anticholinergic activity. Triprolidine provides symptomatic relief in conditions believed to depend wholly, or partly, upon the triggered release of histamine. After oral administration of a single dose of 2.5 mg Triprolidine to adults, the onset of action, as determined by the ability to antagonise histamine-induced wheals and flares in the skin, was within 1 to 2 hours. Peak effects occurred at about 3 hours, and although activity declined thereafter, significant inhibition of histamine-induced wheals and flares still occurred 8 hours after a single dose.

5.3 Pharmacokinetic Properties

Absorption
Triprolidine and codeine are well absorbed from the gut following oral administration.

Metabolism and Elimination

Triprolidine
The plasma half-life ($t_{½}$) of triprolidine was approximately 3.0- 3.3 hours. Animal hepatic microsomal enzyme studies have revealed the presence of several triprolidine metabolites with an oxidized product of the toluene methyl group predominating. In man, it has been reported that only about 1% of an administered dose is eliminated as unchanged triprolidine over a 24-hour period. The apparent total body clearance of triprolidine (Cl/F) was approximately 30 to 37 ml/min/kg. The elimination rate constant (KCl) was approximately 0.26 h-1 h.

Codeine
The plasma half-life ($t_{½}$) of codeine was approximately 3 to 4 hours.

Codeine is metabolised by the liver enzyme CYP2D6 via O-demethylation to form morphine, and via N-demethylation to form norcodeine. Codeine and its metabolites are also glucuronidated and sulphated in the liver.

Individuals who are heterozygous for the CYP2D6*2A allele are classified as ultra-rapid metabolisers of codeine. In these patients CYP2D6 enzyme is induced and O-demethylation of codeine to morphine is increased. If the patient is an extensive or ultra-rapid metabolizer there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses.

After an oral dose, about 86% is excreted in the urine in 24 hours as free drug and metabolites, the majority as metabolites. Trace amounts of codeine are found in the feces. Unchanged drug accounts for 6 to 8% of the dose in urine in 24 hours, which may be increased to about 10% when the urinary pH is decreased.

Pharmacokinetics in Renal Insufficiency
There have been no specific studies Corex T in renal impaired patients.

Pharmacokinetics in Hepatic Insufficiency
There have been no specific studies of Corex T in hepatic impairment.

Pharmacokinetics in the Elderly
There have been no specific studies of Corex T in the elderly.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology and Pharmacology

No long-term studies in animals have been performed with triprolidine or codeine to determine carcinogenic potential or effects on fertility. Triprolidine and codeine have been found to have no mutagenic potential.

Toxicology

Mutagenicity
Triprolidine was not mutagenic in bacterial cells in an Ames test.

Codeine was not mutagenic in bacterial cells *in vitro*, or in an *in vivo* mouse micronucleus test.

Carcinogenicity
Triprolidine and codeine were not carcinogenic in assays performed in mice and rats.

Teratogenicity
Triprolidine did not produce teratogenic effects at oral doses of up to 125 mg/kg/day in the rat, or 100 mg/kg/day in the rabbit.

Codeine did not produce teratogenic effects at oral doses of up to 120 mg/kg/day in the rat, or 30 mg/kg/day in the rabbit. However, at 120 mg/kg/day there was an increase in mortality in rat embryos near the period of implantation.

Fertility
There is no information on the effect of Corex T on human fertility.
No studies have been conducted in animals to determine whether triprolidine or codeine have the potential to impair fertility.

7. DESCRIPTION

Bright reddish orange clear syrupy liquid, free from foreign contaminants

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not known.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Amber colored 50 ml/100 ml PET bottles sealed with ROPP caps.

Bright reddish orange clear syrupy liquid with Pineapple – Menthol like flavour.

8.4 Storage and handling instruction

Store below 25°C. Replace cap securely.

No special requirements for handling.

9. PATIENT COUNSELLING INFORMATION

Corex T cough syrup can cause drowsiness and dizziness. Be careful while driving or operating machinery until you know how Corex T cough syrup affects you. Avoid drinking alcohol while taking Corex T cough syrup as it can cause profound sedation and increase respiratory depression. Inform your doctor if you are pregnant or breastfeeding, Corex T cough syrup is contraindicated. Corex T cough syrup can be habit forming. Take it only for the prescribed duration and do not exceed the recommended dose. Do not take Corex T cough syrup with other cough and cold medicines that contains antihistamines and cough suppressants. Tell your doctor if you are taking any other medicines like Monoamine oxidase inhibitors (MAOIs), antidepressants, sedative and other opioid pain relievers.

10. DETAILS OF MANUFACTURER

Manufactured by:

Pfizer Limited,
Plot No. 47B/2,
Street No.4,I.D.A.,Phase-I
Cherlapally, Hyderabad

Or

Pfizer Limited,
Plot no. 1802-1805, G.I.D.C., Phase III,
VAPI, Dist. Valsad,
Gujarat - 396 195

Or

Pfizer Limited,Khata No. 845/713 and 1108/970/1
34th KM, Tumkur Road,
T - Begur, Nelamangala,
Bangalore Rural - 562 123

Or

Pfizer Limited
Plot No. 9/2, IDA Uppal,
Hyderabad

Marketed in India by:
Pfizer Limited,
The Capital- A Wing,
1802, 18th Floor,
Plot No. C-70, G Block,
Bandra Kurla Complex,
Bandra (East),
Mumbai 400 051,
India.

11. DETAILS OF PERMISSION OR LICENSE NO. WITH DATE:

Mfg. Lic. No. *: 45/RR/AP/2007/F/R(L) dated 23-Apr-2008
Mfg. Lic No. *: G/25A/3864-A dated 24-Nov-2016
Mfg. Lic. No. *: KTK/25A/719/2011 dated 22-Apr-2008
Mfg. Lic. No. *: 38/RR/AP/2010/F/R(L) dated 14-Feb-2025

(*The manufacturing license is renewed every 5 years as per Indian regulations).

12. DATE OF REVISION:

December-2025