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COLDEX

TABLETS. CAPLETS

Composition

Each tablet or caplet contains:

Active Ingredients

Chlorpheniramine maleate	2 mg
Phenylephrine hydrochloride	10 mg
Paracetamol	300 mg
Caffeine	30 mg

Lactose content: 26.5 mg per tablet/caplet.
Sodium content: 0.47-0.7 mg per tablet/caplet.

Other Ingredients

Lactose monohydrate, povidone, sodium starch glycolate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, quinoline yellow aluminium lake, iron oxide yellow, indigo carmine aluminium lake [FD&C blue no.2], colloidal silicon dioxide, magnesium stearate, hydrogenated vegetable oil, Eurdragit E 100.

Action

Coldex is a comprehensive cold preparation, producing rapid and long-lasting relief from cold symptoms.

Chlorpheniramine controls rhinorrhea, sneezing, and itchy and watery eyes associated with elevated histamine levels.

Phenylephrine reduces nasal and sinus congestion.

Paracetamol reduces fever and relieves headache, muscle and joint aches and pains.

Coldex also contains caffeine, to help counteract possible drowsiness from the antihistamine.

Indications

Symptomatic relief of common cold, congestion associated with sinusitis, allergic rhinitis accompanied by fever and pain.

Contraindications

Known hypersensitivity to antihistamines or to any of the components of the preparation.

Patients with severe hypertension, severe coronary artery disease, narrow-angle glaucoma, Closed angle glaucoma, hepatic or severe renal impairment, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal ulceration, and the elderly and debilitated.

Concomitant use with monoamine oxidase (MAO) inhibitors, or within 14 days of discontinuation of such therapy (see Drug Interactions).

Concomitant use of other sympathomimetic decongestants

Phaeochromocytoma

Patients taking tricyclic antidepressants, or beta blocking drugs

During breastfeeding.

Pregnancy - see also Warnings.

Hyperthyroidism, diabetes and heart disease
Do not take this medicine with other paracetamol-containing products
Do not take this medicine with other antihistamine-containing products, including products for relief of colds and coughs

Special Warnings and special precautions for use

Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain paracetamol. These reactions can occur with first-time use of paracetamol or at any time while it is being taken.

Anyone who develops a skin rash or reaction while using paracetamol should **stop the drug** and seek medical attention right away. Anyone who has experienced a serious skin reaction with paracetamol should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

Health care professionals should be aware of this rare risk and consider paracetamol along with other drugs already known to have such an association, when assessing patients with potentially drug induced skin reactions.

Since drowsiness may occur, patients should be warned that their ability to perform potentially-hazardous tasks requiring mental alertness or physical coordination such as driving a vehicle or operating machinery, may be impaired. Children should be warned not to participate in activities such as riding a bicycle or playing near traffic.
As with other antihistamine-containing products, Coldex exerts an anticholinergic (atropine-like) effects and should be used with caution in patients with epilepsy since convulsions may be precipitated; it should also be used with caution in patients with cardiovascular disease, hypertension, bronchitis/bronchial asthma, bronchiectasis, asthma, increased intraocular pressure, hyperthyroidism, hepatic impairment, and diabetes mellitus. Children and the elderly patients are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness).

The effects of alcohol may be increased and therefore should be avoided.(see Drug Interactions).

- The preparation contains paracetamol which may cause liver damage when:
  - Given at a higher than recommended dosage or for a prolonged time.
  - When drinking alcoholic beverages during the treatment period.
  - When taking other medicines that affect liver function.
  - The patient should be informed not to take other medicines to reduce fever and relieve pain, or cold medicines, without consulting a doctor or pharmacist, in order to prevent paracetamol overdose/toxicity.
  - Avoid taking a high dosage (within the recommended limits) of this medicine when fasting.

Coldex should not be used with other antihistamine containing products such as antihistamine containing cough and cold medicines- see also Contraindications .

Due to the antihistamine content, Coldex may cause epigastric distress, and therefore should preferably be taken after meals to diminish gastric irritation.

Accidental poisoning can occur due to the paracetamol content; this may take place in toddlers and infants. Paracetamol-containing products should be kept well out of reach of children.

This product should be administered with care to patients with impaired kidney or liver function.

Potentially fatal hepatotoxicity can result from paracetamol overdosage. However, in rare cases, hepatotoxicity has occurred in patients receiving high or excessive doses within therapeutic doses. Certain patients may be more susceptible to paracetamol hepatotoxicity, e.g., chronic alcoholics, patients with liver disease, or those who are malnourished or taking other drugs that induce hepatic enzymes.

Because of the risk of heptotoxicity, patients should be cautioned against the inadvertent administration of excessive doses of paracetamol by using multiple paracetamol-containing product at once, such as cough and cold remedies, analgesics or arthritic formulations, antipyretics or products for relief of menstrual symptoms or muscle spasm. Administration of paracetamol to children may be especially prone to error due to the many concentrations and strengths of products available. To avoid dosing errors, all product labels should be checked carefully to ensure calculation of the amount of paracetamol to be given.

Medical advice should be sought before using this product in patients with these conditions:
Occlusive vascular disease (e.g. Raynaud's phenomenon)
Cardiovascular disease.
This product should not be used by patients taking other sympathomimetics (such as decongestants, appetite suppressants and amphetamine-like psychostimulants)

The doctor should be consulted prior to performing any type of surgery .

Consumption of large quantities of products containing caffeine (like coffee and tea) may reactivate preexisting duodenal ulcers. High caffeine intake can cause difficulty in sleeping, shaking , and uncomfortable feeling in the chest .

This product contains lactose and may cause allergy in individuals who have intolerance to some sugars)

Use in Pregnancy
Safety of use in pregnancy has not been established.
There are no adequate data for the use of chlorphenamine in pregnant women, the potential risk in humans is unknown. Use during the third trimester may result in reactions in the newborn or premature neonates
This product is not recommended for use in pregnancy due to the phenylephrine and caffeine content. There is a potential increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption during pregnancy.

Use in Breastfeeding
See Contraindications.
Chlorphenamine maleate and other antihistamines may inhibit lactation and may be secreted into the breast milk
. Caffeine in breast milk may have a stimulating effect on breast-fed infants .
Phenylephrine may be excreted in breast milk

Adverse Reactions

Important note:

The elderly are more likely to exhibit adverse reactions.

Adverse reactions to Coldex are usually mild, and in general are due to the antihistamine component. These may include drowsiness, nervousness, restlessness, dizziness, lassitude, giddiness, epigastric distress, dryness of mouth, blurred vision, cardiac palpitations, flushing, increased irritability or excitement (especially in children). Other adverse reactions (related to caffeine) include: nausea, abdominal pain, and diarrhea.

Adverse reactions According to Body System

Central Nervous System

Sedation, somnolence /insomnia, depression, extrapyramidal reactions, dizziness, drowsiness, headache, disturbance in attention, disturbed coordination, confusion, restlessness, excitation, nervousness, anxiety, tremor, irritability, insomnia, paresthesias, neuritis, convulsions, euphoria, hallucinations, hysteria, faintness.

Special Senses

Acute labyrinthitis, blurred vision, diplopia, vertigo, tinnitus.

Gastrointestinal

Epigastric distress/abdominal pain, dyspepsia, dryness of mouth, mouth ulcers, sudden weight loss, anorexia, nausea, vomiting, diarrhea, constipation, sore throat.

Cardiovascular

Hypotension, headache, palpitations, tachycardia, extrasystoles, arrhythmias.

Renal/Genitourinary

Urinary frequency, difficult urination, urinary retention, early menses.

Papillary renal failure has been reported following consumption of large amounts of paracetamol. Renal tubular necrosis has been associated occasionally with hepatic injury produced by paracetamol overdose.

Respiratory

Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness, dryness of nose and throat.

Hematological

Hemolytic anemia, neutropenia, thrombocytopenia purpura, leukopenia, agranulocytosis.

Hepatobiliary disorders:

Hepatitis including jaundice, hepatotoxicity , hepatic dysfunction .

Skin and subcutaneous disorders:

Exfoliative dermatitis, rash, urticaria, photosensitivity,

Musculoskeletal and connective tissue disorders

Muscular twitching, muscular tremor , muscle weakness.

Renal: nephropathy, including

Hypersensitivity/Allergic Reactions: reactions including skin eruptions, skin rashes, urticaria, photosensitivity, angioedema and Stevens Johnson syndrome, toxic epidermal necrolysis, laryngeal edema, bronchospasm, and/or anaphylaxis have occurred rarely. Dose-dependent cross-sensitivity to paracetamol may occur in aspirin-sensitive asthmatics. Low initial doses of paracetamol (less than 1000 mg) are recommended in these patients, with monitoring for about 3 hours following initial doses.

Other hypersensitivity reactions include:
Difficulty breathing; closing of the throat; swelling of lips, tongue, or face; or hives, seizures; unusual behavior or hallucinations; or an irregular or fast heartbeat.
Less serious side effects may be more likely to occur: dizziness, lightheadedness, or drowsiness; headache; insomnia; anxiety ; tremor (shaking) or restlessness; increased blood pressure, diarrhoea, nausea or vomiting; or sweating.

Miscellaneous adverse reactions
Fatigue, chills,, fever.

Adverse Reactions identified during post-marketing use for combination products containing paracetamol, caffeine, and phenylephrine HCl are listed below. The frequency of these reactions is unknown

Eye disorders
Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma

Cardiac disorders
Tachycardia, palpitations

Skin and subcutaneous disorders
Allergic reactions (e.g. rash, urticaria, allergic dermatitis).
Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics.

Renal and urinary disorders
Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

Drug Interactions
Coldex/Alcohol/CNS Depressants (including Tricyclic Antidepressants):
Additive effects may take place when Coldex is used concurrently with alcohol or other CNS depressants, e.g. hypnotics, sedatives, tranquilizers, antianxiety agents, narcotic analgesics, anticonvulsants, general anesthetics, other antihistamines.
***Coldex/ Ototoxic Medications*:** Symptoms of ototoxicity may be masked if used concurrently with ototoxic medications, particularly aminoglycoside antibiotics such as amikacin, dihydrostreptomycin, gentamicin, kanamycin, neomycin, streptomycin, tobramycin, and viomycin.
***Coldex/Anticholinergic Agents or Other Agents Possessing Anticholinergic Activity**:* Concurrent use may lead to a potentiation of the anticholinergic effects (such as atropine). Therefore caution should be exercised and patients should be advised to promptly report occurrence of gastrointestinal problems, since paralytic ileus may occur upon concurrent therapy of antihistamines and anticholinergic agents.
Coldexd/Phenytoin: Phenytoin metabolism is inhibited by the chlorphenamine component and this can cause phenytoin toxicity
Coldex/Oral Anticoagulants: Regular administration of Coldex may enhance the activity of coumarin anticoagulants (due to the paracetamol content) when given concurrently. Occasional doses have no significant effect.
Coldex/Hepatic Enzyme-Inducing Agents (e.g., Barbiturates, Carbamazepine, Phenytoin)/ Hepatotoxic Medications/Alcohol: Concurrent administration of enzyme inducers may decrease the therapeutic effect of paracetamol in the product, probably because of increased metabolism resulting from induction of hepatic microsomal enzyme activity.
The risk of hepatotoxicity with single toxic doses or prolonged use of high doses of paracetamol may be increased in patients consuming alcoholic beverages or in patients taking other hepatotoxic medications.

Coldex/Salicylates/ Other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Chronic high-dose administration of paracetamol with salicylates and/or other non-steroidal anti-inflammatory drugs increases the risk of analgesic nephropathy.

Coldex/Zidovudine: The paracetamol component may competitively inhibit the hepatic glucuronidation and decrease the clearance of zidovudine. Zidovudine may also inhibit the hepatic glucuronidation of paracetamol. Concurrent use should be avoided, because the toxicity of either or both medications may be potentiated.

Coldex/Lopinavir: Lopinavir may increase the plasma concentration of chlorphenamine .

Colex/Cholestyramine: Cholestyramine may reduce the absorption of paracetamol. Oral doses of cholestyramine and paracetamol should be given at least 1 hour apart.

Coldex/Metoclopramide/Domperidone: The speed of absorption of paracetamol may be increased by metoclopramide or domperidone.

Coldex/ MAO inhibitors: Concurrent use may prolong and intensify the anticholinergic effects of antihistamines and the effects of sympathomimetics. Severe hypertensive reactions may occur when sympathomimetics are given to patients receiving MAO inhibitors (see Contraindications).

Coldex/ Adrenergic Bronchodilators/ Caffeine-Containing Medications/ Caffeine-Containing Beverages: Due to the caffeine content of the preparation, concomitant administration may result in additive CNS stimulation.

Coldex/Anticholinergic Agents or Other Agents Possessing Anticholinergic Activity: Because of the antihistamine component present in Coldex, concurrent use may lead to a potentiation of the anticholinergic effects. Therefore caution should be exercised and patients should be advised to promptly report occurrence of gastrointestinal problems, since paralytic ileus may occur upon concurrent therapy of antihistamines and anticholinergic agents.

Coldex/Bronchodilators/Caffeine Containing Beverages: Due to the caffeine content concomitant administration may result in additive CNS stimulation. Too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.

Coldex/ β-Blockers: β-Blockers increase the effects of sympathomimetics.

Coldex/ α-Blockers: The vasopressor response to phenylephrine is decreased by prior administration of an adrenergic blocking agent

Coldex/Oxytocic Drugs: When a vasopressor, e.g. phenylephrine , is used in conjunction with oxytocic drugs, the pressor effect is potentiated.

Coldex/Sympathomimetic Agents: Combination products containing phenylephrine and a bronchodilator sympathomimetic agent should not be used concomitantly with epinephrine or other sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) because tachycardia or other serious arrhythmias may occur.

Coldex/General Anesthetics: Rarely, administration of phenylephrine to patients who have received cyclopropane or halogenated hydrocarbon general anesthetics that increase cardiac irritability and seem to sensitize the myocardium to phenylephrine may result in arrhythmias. Vasopressors should therefore be used only with extreme caution or not at all with these general anesthetics.

Coldex/Monoamine Oxidase (MAO) Inhibitors : The cardiac and pressor effects of phenylephrine are potentiated by administration of monoamine oxidase (MAO) inhibitors because metabolism of phenylephrine is reduced. Oral administration of phenylephrine to patients receiving a MAO inhibitor should be avoided. In addition, concurrent administration may prolong and intensify the anticholinergic (drying) effects of the antihistaminic component. Therefore concurrent use of Coldex with monoamine oxidase (MAO) inhibitor therapy or within 14 days of discontinuation of such therapy is contraindicated (see Contraindications).

Coldex/Tricyclic Antidepressants : Tricyclic antidepressants may potentiate the vasopressor effects of phenylephrine component.

Coldex/Atropine: Atropine sulfate may block the reflex tachycardia caused by phenylephrine and enhances the pressor response to phenylephrine.

Coldex/Injectable Ergot Alkaloid: An excessive rise in blood pressure may occur if phenylephrine-containing product is administered to patients receiving a parenteral injection of an ergot alkaloid such as ergonovine maleate.
Coldex/Digitalis: The possibility that digitalis can sensitize the myocardium to the effects of sympathomimetic drugs should be considered.
Coldex/ Furosemide or Other Diuretics: Administration of furosemide or other diuretics may decrease arterial responsiveness to vasopressors such as phenylephrine.

Diagnostic Interference

Due to the antihistamine component, Coldex should be discontinued about 4 days prior to skin testing procedures, since it may prevent otherwise positive reactions to dermal reactivity indicators.

The paracetamol component in this product may produce false-negative test results for urinary 5-hydroxy- indoleacetic acid.

Dosage and Administration

Adults: 1 tablet or caplet every 4 hours, with meals.

Children 6-12 Years of Age: 1 tablet or caplet, 3 times daily.

Overdosage

For Paracetamol
Manifestations

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

In massive overdosage, paracetamol may cause hepatic toxicity. In adults and adolescents, hepatic toxicity has been rarely reported following ingestion of acute overdose of less than 7.5 –10 g. Fatalities are infrequent (less than 3-4% of untreated cases) and have been rarely reported with overdoses of less than 15 g. Early symptoms following a potentially hepatotoxic overdose may include nausea, vomiting, stomach pain, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48-72 hours post-ingestion.

Serious toxicity or fatalities are extremely infrequent in children, possibly due to differences in the way they metabolize paracetamol. An acute overdosage of less than 150 mg/kg bodyweight in children has not been associated with hepatic toxicity.

Treatment
Adults and Adolescents

Regardless of the quantity of paracetamol reported or assumed to have been ingested, N-acetylcysteine should be administered immediately, if 24 hours or less have elapsed from the time of ingestion.

An initial dose of 150 mg N-acetylcysteine/kg body weight is infused I.V. in 200 ml of 5% Dextrose Injection over 15 minutes. This is followed by I.V infusion of 50 mg N-acetylcysteine/kg body weight in 500 ml of 5% Dextrose Injection over the next 4 hours, and 100 mg N-acetylcysteine/kg body weight in 1 liter of 5% Dextrose Injection over the next 16 hours (providing a total dose of 300 mg/kg body weight of N-acetylcysteine over 20 hours).

In addition to N-acetylcysteine administration, it is recommended that the stomach be emptied promptly by lavage, or by induction of emesis with syrup of ipecac.

A serum paracetamol assay should be obtained as early as possible, but not less than 4 hours following ingestion. If plasma level falls above the lower treatment line on the paracetamol overdose nomogram, acetylcysteine therapy should be continued.

Liver function tests should be performed initially, and repeated at 24-hour intervals.

Children

Induce emesis using syrup of ipecac.

A serum paracetamol assay should be obtained as soon as possible, but not less than 4 hours following ingestion.

If more than 150 mg/kg body weight or an unknown amount was ingested, plasma paracetamol level should be obtained.

The plasma paracetamol level should be obtained as soon as possible, but no sooner than 4 hours following ingestion. If plasma level falls above the lower treatment line on the paracetamol overdose nomogram, the acetylcysteine therapy should be initiated and continued for a full course of therapy. If a paracetamol assay is not available and the paracetamol ingestion exceeds 150 mg/kg body weight, N-acetylcysteine therapy should be initiated and continued for a full course.

The dosage and administration of N-acetylcysteine in children is the same as recommended for adults and adolescents. However, the quantity of I.V. fluid used in children should be modified, taking into account both age and weight.

For Chlorpheniramine Maleate

Manifestations

Antihistamine overdosage reactions may vary from central nervous system depression to stimulation, especially in children. Atropine-like signs and symptoms such as dry mouth, fixed dilated pupils and flushing, as well as gastrointestinal symptoms, may occur.

Treatment

There is no specific therapy for acute overdosage with antihistamines. General symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Conscious Patients

Vomiting should be induced even though it may have occurred spontaneously. If the patient is unable to vomit, gastric lavage is indicated. Isotonic saline is the lavage of choice. Adequate precautions must be taken to protect against aspiration, especially in infants and children.

Charcoal slurry or another suitable agent should be instilled into the stomach after vomiting or lavage. Saline cathartics or milk of magnesia may be of additional benefit.

Unconscious Patients

The airway should be secured with a cuffed endotracheal tube before attempting to evacuate the gastric contents. Intensive supportive and nursing care are indicated, as for any comatose patient.

Do not administer CNS stimulants.

Hypotension is an early sign of impending cardiovascular collapse. If a vasopressor agent is needed, noradrenaline, phenylephrine or dopamine is indicated. Use of adrenaline should be avoided since it may worsen hypertension. In case of convulsions, diazepam may be used and repeated as necessary.

When life-threatening CNS signs and symptoms are present, intravenous physostigmine salicylate may be considered.

Ice packs and cooling sponge baths, but not alcohol, can help in reducing the fever commonly observed in children.

Hemoperfusion may be used in severe cases.

For Caffeine)

Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

No specific antidote is available, but supportive measures may be used.

For Phenylephrine

Overdosage of phenylephrine may cause hypertension and possibly reflex bradycardia, headache, seizures, cerebral hemorrhage, palpitations, paresthesia, or vomiting. Headache may be a symptom of hypertension. In severe cases confusion, hallucinations, seizures and arrhythymia may occur. However the amount required to produce serious phenylephrine toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Hypertension may be relieved by administration of an α-adrenergic blocking agent (e.g. phentolamine).

Drug Registration No.:

Tablets: 069 84 28596 00
Caplets: 059 74 21484 00

Storage

Store in a dark place below 25°C.

Manufacturer

Teva Pharmaceutical Industries Ltd
P.O.Box 3190, Petach Tikva.