Zedex Plus

To be sold by retail on the prescription of a Registered Medical Practioner Only

1. Generic Name:

Dextromethorphan Hydro bromide, Chlorpheniramine Maleate and Phenylephrine hydrochloride Syrup

2. Qualitative and quantitative composition:

Each 5ml of Zedex Plus syrup consists of

Dextromethorphan hydro bromide IP : 10 mg

Chlorpheniramine maleate IP: 2mg

Phenylephrine hydrochloride IP: 5 mg

Flavoured syrup base q.s.

3. Dosage form and strength:

Adults and children >12 years -10ml 2-3 times/day

Children (6-12 yrs) – 5ml 2-3 times/day

4. Clinical particulars:

4.1 Therapeutic Indications

For the treatment of common cold and cough

4.2 Posology and Method of Administration

For oral administration only. Do not exceed the stated dose or frequency of dosing.

It should not be used with other cough and cold medicines. Reassess patient, if symptoms persist more than 7 days.

Doses as below or as directed by physician.

Adults and children >12 years -10ml 2-3 times/day

Children (6-12 yrs) – 5ml 2-3 times/day

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/1.73m2

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.

4.3 Contraindications

Hypersensitivity to any of the ingredients.

Also contraindicated in patients with hyperthyroidism, moderate-severe hypertension; ventricular tachycardia; severe coronary artery disease; narrow-angle glaucoma; urinary retention and prostatic hypertrophy; peptic ulcer; emphysema; chronic bronchitis;

It should not be used as treatment for lower respiratory tract conditions including asthma and during an asthma attack

It should not be used in patients on MAO inhibitor therapy (or for 14 days after stopping MAOI therapy).

4.4 Special warnings and precautions for use

Use with caution in the presence of cardiac disorders, diabetes or peripheral vascular disease.

Pregnancy (Category C)

It is not known whether Zedex Plus Syrup can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, Zedex plus Syrup should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zedex Plus Syrup is administered to a nursing woman.

Paediatric Use

Safety and effectiveness in the pediatric population, under 6 years, have not been established.

It should be avoided in productive cough or cough with sputum

Caution should be exercised before administering Zedex Plus 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.
- Slow metabolizers of CYP2D6 or concomitant user of CYP2D6 inhibitors -Dextromethorphan is metabolised by hepatic cytochrome P450 2D6, whose activity is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Caution is needed in them as they may experience exaggerated and/or prolonged effects of dextromethorphan
- Patients with history of drug abuse-Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with 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.
- Zedex plus should not be used with other cough and cold medicines and other anti-histamine containing products.
- With caution-Due to its Chlorpheniramine content which has anticholinergic effects, it should be used with caution in epilepsy, severe hypertension and cardiovascular disease, raised intraocular

pressure including glaucoma, prostatic hypertrophy, bronchitis, bronchiectasis and bronchial asthma.

- Children and the elderly are more likely to experience neurological anticholinergic effects and paradoxical excitation of Chlorpheniramine (e.g. increased energy, restlessness, nervousness).
- While driving and using machinery
- Avoid use in elderly patients with confusion.
- Maximum recommended dose or frequency of dosing should not be exceeded.
- Keep out of reach of children

4.5 Drugs interactions

Alcohol, barbiturates (eg, phenobarbital), tricyclic antidepressants (eg, amitriptyline), other CNS depressants -effects may be enhanced by chlorpheniramine.
Anesthesia (eg, halothane) -may cause serious cardiac arrhythmias.
Antihypertensives (eg, methyldopa, reserpine, veratrum alkaloids) -Antihypertensive effects may be reduced by phenylephrine.
Beta-adrenergic blockers -may potentiate the effects of phenylephrine.
MAOIs (eg, isocarboxazid) -may prolong and intensify the anticholinergic effects of chlorpheniramine and increase the effects of phenylephrine. Dextromethorphan is contraindicated with MAOIs or within 2 week of discontinuing MAOI therapy.
Opioid antitussives (eg, codeine) -may increase the cough suppressant effects of dextromethorphan.
Laboratory Test Interactions-may interfere with diagnostic test results for skin tests using allergen extracts.

Chlorpheniramine Maleate-

- Chlorpheniramine inhibits phenytoin metabolism and can lead to phenytoin toxicity.
- The anticholinergic effects of Chlorpheniramine are intensified by MAOIs

Dextromethorphan-

- Opioid antitussives (eg. codeine)-may increase the cough suppressant effects of dextromethorphan.
- 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.
  - 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.

Phenylephrine-

- It may cause severe drug interaction with Iobenguane, isocarboxazid, linezolid, phenelzine,procarbazine,selegiline transdermal, tranylcypromine.

4.6 Use in Special Populations

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Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zedex Plus Syrup is administered to a nursing woman.

Pediatric Use

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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

The components of Zedex Plus are well tolerated and adverse effects are rare, transient and usually self- limiting.

Adverse events may include dizziness, drowsiness, dry mouth, headache, sleep disturbances, palpitations, rashes or itching, and GI disturbance like nausea-vomiting, constipation, heartburn or anorexia.

Dryness of nose and throat,thickening of bronchial secretions and nasal stuffiness maybe seen.

Rarely seen are Cardiac arrhythmias, fluctuations in blood pressure with flushing or pallor, anxiety, confusion, convulsions, disturbed coordination, dysphoria, euphoria, excitation (especially in children), fatigue, hallucinations, hysteria, tinnitus, irritability, nervousness, neuritis, paraesthesia, restlessness, trembling, tremor, vertigo, weakness, Difficult urination, early menses, polyuria, urinary frequency

Very rarely seen are shortness of breath, chest tightness, Hematologic effects like Agranulocytosis, hemolytic anemia, hypoplastic anemia, thrombocytopenia or Chills, and Hypersensitivity-anaphylactic shock.

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

(A) Chlorpheniramine Maleate

Adverse reactions identified in literature 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 System organ class Adverse Reaction Frequency of some reactions is unknown but likely to be rare or very rare.

It can cause Sedation, somnolence,disturbance in attention, abnormal coordination, dizziness, headache, blurred vision, nausea, dry mouth, fatigue.Sometimes it may cause Vomiting, abdominal pain, diarrhoea, dyspepsia, Allergic reactions, angioedema, anaphylactic reactions, Chest tightness, Anorexia, Muscle twitching, muscle weakness, Confusion, excitation, irritability, nightmares, paradoxical excitation(increased energy, restlessness, nervousness), Urinary retention, exfoliative dermatitis, rash, urticaria, photosensitivity, Thickening of bronchial secretions, hypotension. (Children and the elderly are more susceptible to neurological anticholinergic effects and paradoxical excitation)

(B) Dextromethorphan:

Nervous system disorders-drowsiness, dizziness, 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.

Gastrointestinal disorders-gastrointestinal disturbance, nausea, vomiting, abdominal discomfort

Skin and subcutaneous disorders- allergic reactions (e.g. rash, urticaria, angioedema)

(C) Phenylephrine

It may cause fast, pounding or irregular heartbeat, severe dizziness or nervousness, sleep problems like insomnia, increased blood pressure--severe headache, blurred vision, pounding in your neck or ears. It may cause flushing, loss of appetite, feeling restless or excited (especially in children).

4.9 Overdose

Signs and Symptoms

Overdosage with Dextromethorphan HBr and Antihistamines may produce CNS excitement and mental confusion. In the small child, symptoms include excitation, hallucination, ataxia, incoordination, tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma and death may occur in very severe cases. In the adult, fever and flushing are uncommon; excitement leading to convulsions and postictal depression is often preceded by drowsiness and coma. Respiration is usually not seriously depressed; blood pressure is usually stable.

Overdosage with sympathomimetic amines can cause hypertension, headache, convulsions, cerebral haemorrhage and vomiting. Premature ventricular beats and short paroxysms of ventricular tachycardia may also occur. Headache may be a symptom of hypertension. Bradycardia may also be seen early in phenylephrine overdosage through stimulation of baroreceptors. Excessive CNS stimulation may result in excitement, tremor, restlessness, and insomnia. Other effects may include pallor, mydriasis, hyperglycemia, and urinary retention. Severe overdosage may cause tachypnea, or hypernea, hallucinations, convulsions, or delirium, but in some individuals, there may be CNS depression. Arrhythmias (including ventricular fibrillation) may lead to hypotension and circulatory collapse. Severe hypokalemia can occur, probably due to compartmental shift rather than depletion of potassium.

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.

If required, the patient should be induced to vomit (pharmacologic vomiting is the preferred method; by the administration of ipecac syrup), unless the patient is comatose, convulsing or has lost the gag reflex, in which case gastric lavage should be performed using a large bore tube. If indicated, follow with activated charcoal and a saline cathartic. Precautions must be taken against aspiration, especially in infants, children and comatose patients

5. Pharmacological properties

5.1 Mechanism of Action

Dextromethorphan hydrobromide, is an anti tussive and acts centrally to elevate the threshold for coughing. It has no analgesic or addictive properties. The onset of antitussive action occurs in 15 to 30 minutes after administration.

Chlorpheniramine maleate is an anti histaminic with anticholinergic action.It competitively antagonizes most of the smooth muscle stimulation actions of histamine on the H1 receptors of the GI tract, uterus, large blood vessels and bronchial muscle and antagonizes the action of histamine that results in increased capillary dilatation, permeability, formation of edema and irritation of nerve endings. It reduces peripheral histamine induced stimulation of cough receptors and also acts by binding to CNS receptors to control cough excitability.

Phenylephrine hydrochloride acts predominantly by a direct action on post synaptic alpha adrenergic receptors. In therapeutic doses, the drug has no significant stimulant effect on the beta adrenergic receptors of the heart. Following oral administration, constriction of blood vessels in the nasal mucosa may relieve nasal congestion. In therapeutic doses, the drug causes little, if any, central nervous system stimulation.

5.2 Pharmacodynamic properties

Dextromethorphan hydrobromide - acts centrally to elevate the threshold for cough. It has no analgesic or addictive properties. The onset of antitussive action occurs in 15 to 30 minutes after administration.

Chlorpheniramine maleate- competitively antagonizes most of the smooth muscle stimulation actions of histamine on the H1 receptors of the GI tract, uterus, large blood vessels and bronchial muscle and antagonizes the action of histamine that results in increased capillary dilatation, permeability, formation of oedema and irritation of nerve endings. It reduces peripheral histamine induced stimulation of cough receptors and also acts by binding to CNS receptors to control cough excitability.

Phenylephrine is an alpha-1 adrenergic agonist that raises blood pressure, it dilates the pupils and causes local vasoconstriction. Ophthalmic formulations of phenylephrine act for 3-8 hours while intravenous solutions have an effective half life of 5 minutes and an elimination half life of 2.5 hours.

5.3 Pharmacokinetic properties

Dextromethorphan has a low oral absorption of 11% with a protein binding of 60-70%. It is metabolized by hepatic enzymes, majorly CYP 2D6 and excreted by kidneys. Half life is about 4-5 hours

Chlorpheniramine maleate has an oral bioavailability of 25-50% with a protein binding of 72%. It is metabolized by hepatic enzymes, majorly CYP 2D6 and excreted by kidneys.

Phenylephrine has an oral bioavailability of 38% with a protein binding of 95%. It is metabolized by hepatic monoamine oxidase enzymes, and excreted by kidneys. Half life is about 3.5 hours.

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 and has around 11% oral absorption.

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. Dextromethorphan has a low a protein binding of 60-70%.

Metabolism

Chlorpheniramine Maleate -Chlorpheniramine undergoes considerable first-pass metabolism. Chlorphenamine is extensively metabolized via demethylation in the liver, forming desmethyl - and didesmethylchlorphenamine. It is metabolized by hepatic enzymes, majorly CYP 2D6.

Dextromethorphan is metabolized by hepatic enzymes, majorly CYP 2D6 and excreted by kidneys. It 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-Nmethylmorphinan), 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-half-life varies from 2 to 43 hours. Unchanged drug and metabolites are excreted mainly in urine. Considerable inter subject variation (two- to fivefold difference in urinary metabolite excretion) in Chlorpheniramine metabolism is found.

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. Half-life is about 4-5 hours. 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.

Phenylephrine

Absorption

Phenylephrine is 38% orally bioavailable. Clinically significant systemic absorption of ophthalmic formulations is possible, especially at higher strengths and when the cornea is damaged.

Metabolism

Phenylephrine is mainly metabolized by monoamine oxidase A, monoamine oxidase B, and SULT1A. The major metabolite is the inactive meta-hydroxymandelic acid, followed by sulfate conjugates. Phenylephrine can also be metabolized to phenylephrine glucuronide.

Elimination

86% of a dose of phenylephrine is recovered in the urine with 16% as the unmetabolized drug, 57% as the inactive meta-hydroxymendelic acid, and 8% as inactive sulfate conjugates.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Non-Clinical safety data on Chlorpheniramine maleate, phenylephrine and dextromethorphan obtained from the literature have not revealed findings which are of relevance to the recommended dosage and use of the product.

7. Description

Zedex Plus syrup is a combination of the following:

Dextromethorphan, chemically known as Morphinan, 3-Methoxy-17-methyl-, (9α, 13α, 14α) - hydrobromide, is a centrally acting cough suppressant.

Chlorpheniramine maleate, chemically known as 2-Pyridinepropanamine, γ-(4-chlorophenyl)-N, N-dimethyl-, (Z)-2-butenedioate (1:1), is a H1 receptor antihistamine which suppresses sneezing, running nose and nasal irritation

Phenylephrine, chemically known as Benzenemethanol, 3-hydroxy-α-[(methylamino)methyl]-, hydrochloride (R), is an alpha receptor agonist and constricts nasal vessels to reduce congestion

8. Pharmaceutical particulars:

8.1 Incompatibilities

No incompatibilities have been identified

8.2 Shelf-life

24 Months

8.3 Packaging information

100 ml Bottle

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light and moisture. Keep the medicine out of the reach of children.

9. Patient Counselling Information:

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

10. Details of manufacturer

Manufactured in India by

WOCKHARDT LIMITED

Plot No. 57, Village Kunjhal,

P.O. Barotiwala,Teh. Baddi,

Distt. Solan (H.P.) - 174103.

11. Details of permission or licence number with date

MNB/ 05/107

12. Date of revision

23/03/21

PvPI Helpline No. 1800-180-3024'