DESCRIPTION

XEED-4: The fixed dose combination (FDC) contains Isoniazid (in modified-release form) which is isonicotinyl hydrazide, Rifampicin, which is 3-[(4-Methyl-1-piperazinyl)imino]methyl]rifamycin, Pyrazinamide, which is pyrazine-2-carboxamide and Ethambutol Hydrochloride, which is (S S)-N,N'-ethylenbis (2-aminobutan-1-ol)dihydrochloride.

XEED-4 is available as brown coloured, oblong, biconvex, film coated tablet, plain on both sides.

XEED-3E: The fixed dose combination (FDC) contains Isoniazid (in modified-release form) which is isonicotinyl hydrazide, Rifampicin, which is 3-[(4-Methyl-1-piperazinyl)imino]methyl]rifamycin and Ethambutol Hydrochloride, which is (S S)-N,N'-ethylenbis (2-aminobutan-1-ol)dihydrochloride.

XEED-3E is available as brown coloured, oblong, biconvex, film coated tablet, plain on both sides.

XEED-2: The fixed dose combination contains Isoniazid (in modified-release form) which is isonicotinyl hydrazide and Rifampicin which is 3-[(4-Methyl-1-piperazinyl)imino]methyl]rifamycin.

XEED-2 is available as brown coloured, oblong, biconvex, bevel edged, film coated tablet, plain on both sides.

COMPOSITION

XEED-4

Each film coated tablet contains:

- Rifampicin IP ........................................ 150mg
- Pyrazinamide IP .................................... 400mg
- Ethambutol Hydrochloride IP .................... 275mg
- Isoniazid IP .......................................... 75mg (In modified - release form)

Colours: Ferric Oxide and Titanium Dioxide

XEED-3E

Each film coated tablet contains:
Rifampicin IP ........................................150mg
Ethambutol Hydrochloride IP................. 275mg
Isoniazid IP.......................................... 75mg (In modified-release form)

Colours: Ferric Oxide and Titanium Dioxide

XEED- 2

Each film coated tablet contains:

Rifampicin IP......................................... 150mg
Isoniazid IP........................................... 75mg (In modified - release form)

Colours: Ferric Oxide and Titanium Dioxide

PHARMACOLOGICAL CLASSIFICATION
Anti-tubercular drug

PHARMACOLOGICAL ACTION
XEED is a range of antitubercular fixed dose combinations of four first line agents used in the treatment of tuberculosis. Rifampicin, and Pyrazinamide are bactericidal antituberculosis agents. Isoniazid is bacteriostatic for semi-dormant bacilli and bactericidal for rapidly dividing microorganisms. Ethambutol is a bacteriostatic antitubercular agent.

CLINICAL EXPERIENCE
An open labelled, randomized two period crossover study was done in 24 healthy male volunteers. In this study, relative bioavailability of Rifampicin and Isoniazid from four drug FDC formulation (wherein Isoniazid is modified -release) was compared to reference conventional formulation consisting of 4 individual drugs (in loose combination) given together as single dose. Extent of absorption (AUC) and peak plasma concentration (Cmax) of Isoniazid from the fixed dose combination (wherein Isoniazid is modified-release ) were comparable to AUC and Cmax of reference conventional release Isoniazid formulation. However, Cmax and AUC of Rifampicin from conventional release combination formulation were found to be significantly lower than the formulation containing modified-release Isoniazid , as the possible interaction between Isoniazid and Rifampicin has been avoided in the fixed dose formulation wherein Isoniazid release has been modified. The AUC of Rifampicin from the formulation having Isoniazid in modified-release form after single dose administration was 42.48 compared to 29.92 from conventional combination (loose drugs given together).

Formulation Design
XEED range of fixed dose combinations are based on a special tablet-in-tablet design. This design offers a unique way to prevent the loss of bioavailability of Rifampicin in presence of Isoniazid due to their well known interaction. This interaction has been prevented by spatial control of release of both the drugs in such a way that their release takes place at different locations of GIT. Rifampicin releases in acidic pH of stomach and gets absorbed immediately whereas Isoniazid is released in the proximal part of intestine where pH rises above 5.0. Thus, Rifampicin and Isoniazid do not come in contact with each other in solution stage in the acidic pH of gastric region, thereby, preventing the degradation of Rifampicin. XEED offers optimal bioavailability of Rifampicin and other antitubercular drugs administered in the fixed-dose combination.

INDICATION
XEED-4: For the initial phase of new smear +ve cases of pulmonary TB ; new smear -ve cases of pulmonary TB with extensive parenchymal involvement and new severe cases of extra pulmonary
TB. Additionally for initial phase of previously treated (smear +ve) relapse, treatment failure and interruption of pulmonary TB treatment.2

XEED-3E: For the continuation phase of previously treated smear positive, relapse, treatment failure, interruption of pulmonary TB treatment cases.2

XEED-2: For the continuation phase of new smear +ve cases of pulmonary TB; new smear -ve cases of pulmonary TB with extensive parenchymal involvement and new severe cases of extrapulmonary TB. Additionally for continuation phase of new smear -ve (other than category 1 patients) PTB and new less severe forms of extrapulmonary TB.2

CONTRA-INDICATIONS
XEED fixed dose antitubercular combination tablets (XEED-4, XEED-3E and XEED-2) are contraindicated in patients with hypersensitivity to Rifampicin, Isoniazid, Pyrazinamide and Ethambutol.
Contraindicated in the presence of jaundice or any other pre-existing liver disorders.
Contraindicated in patients with optic neuritis.
Not to be used in children under the age of thirteen.
Safety in pregnancy has not been established.
All agents of Xeed combination tablets are excreted in breast milk. Safety during lactation has not been established.

WARNINGS
Caution should be observed with the use of XEED range of fixed dose antitubercular combination tablets in the following patients:

- Impaired kidney function: Dosage adjustment may be required according to the serum concentrations of Ethambutol (not applicable to XEED-2)
- Patients with impaired hepatic function (see "Special Precautions")
- Elderly patients
- Patients with visual defects.
- Patients at a risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic or pregnant: pyridoxine supplementation (in a 10 mg to 50 mg daily dose) is usually required in these instances
- Patients with a history of gout
- Rifampicin may decrease the effect of oral contraceptives and patients are advised to change to non-hormonal methods of birth control
- Epileptic patients: Isoniazid may precipitate seizures

DOSAGE AND DIRECTIONS FOR USE3
The recommended dosage schedule for XEED-4 (2 months initial phase)

<table>
<thead>
<tr>
<th>Patient's body weight (Kg)</th>
<th>Initial phase (2 months) XEED-4 Daily Dosage (No. of Tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 37</td>
<td>2</td>
</tr>
<tr>
<td>38 - 54</td>
<td>3</td>
</tr>
<tr>
<td>55 - 70</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 71</td>
<td>5</td>
</tr>
</tbody>
</table>

The tablet should be swallowed whole (with water) and is not to be chewed, one hour before or 2 hours after a meal.

The recommended dosage schedule for XEED-3E (5 months continuation phase)
### (Kg) | Daily Dosage (No. of Tablets) (5 months) XEED-3E
---|---
30 - 37 | 2
38 - 54 | 3
55 - 70 | 4
> 71 | 5

The tablet should be swallowed whole (with water) and is not to be chewed, one hour before or 2 hours after a meal.

### The recommended dosage schedule for the 4 month continuous phase (XEED-2)

| Patient's body weight (Kg) | Daily Dosage (No. of Tablets) Continuation phase (4 months) XEED-2 |
---|---|---|
30 - 37 | 2 |
38 - 54 | 3 |
55 - 70 | 4 |
> 71 | 5 |

The tablet should be swallowed whole (with water) and is not to be chewed, one hour before or 2 hours after a meal.

## SIDE EFFECTS AND SPECIAL PRECAUTIONS

Gastrointestinal: Nausea, vomiting, anorexia, diarrhoea, abdominal pain.

Hypersensitivity reactions: Fever, pruritis, skin eruptions, soreness of the mouth and tongue, lymphadenopathy, vasculitis.

Neurological effects: Headache, drowsiness, dizziness, visual disturbances, peripheral neuritis, muscular weakness, psychotic reactions, convulsions (usually in patients with prior history of seizures); optic neuritis and atrophy.

### Rifampicin

Some patients experience cutaneous reactions such as facial flushing, itching, rash, or less frequently, eye irritation 2 to 3 hours after a daily dose. A 12-hour “flu” syndrome of fever, chills and malaise has been associated with intermittent administration.

Pseudomembranous colitis has been reported. Hepatitis occurs less frequently. Alterations in kidney and liver function have occurred.

Thrombocytopenia, eosinophilia, transient leucopenia and haemolytic anaemia have been reported to occur. Development of autoimmune thrombocytopenia is indication for its permanent discontinuation.

XEED range of fixed dose antitubercular combination tablets may cause an orange-red discoloration of faeces, saliva, sputum, tears, urine and other body fluids. Patients are warned that soft contact lenses may be permanently discoloured.

### Isoniazid

Patients that are slow inactivators of Isoniazid have a higher incidence of certain side effects. Peripheral neuropathy is a common side effect, especially in patients with poor nutrition, as is rash, fever and jaundice.

Haematological effects: various anaemias; agranulocytosis; thrombocytopenia; eosinophilia. Other side effects: hyperglycaemia; metabolic acidosis; lupus-like syndrome; rheumatoid syndrome; urinary retention; methaemoglobinemia; tinnitus; gynaecomastia; pellagra. The prophylactic administration of pyridoxine prevents the development of peripheral neuritis as well as most other nervous system dysfunctions.

### Pyrazinamide

The most serious side effect is hepatotoxicity and its frequency appears to be dose-related. Hyperuricaemia commonly occurs (occasionally accompanied by arthralgia) and may lead to attacks of gout. Development of gout is indication for its permanent discontinuation.

Other side effects: arthralgia; malaise; fever; sideroblastic anaemia; dysuria. Photosensitivity and skin rash have been reported less frequently.
**Ethambutol Hydrochloride**

The most important adverse effect is retrobulbar neuritis with a reduction in visual acuity, which appears to be dose-related; constriction of visual field; central or peripheral scotoma and green-red colour blindness affecting one or both eyes. Development of optic neuritis is indication for its permanent discontinuation. 

Renal clearance of urate may be reduced and acute gout may be precipitated.

Other side effects. Leucopenia; disorientation; hallucinations; jaundice; transient liver dysfunction; peripheral neuritis; metallic taste.

**SPECIAL PRECAUTIONS**

In the following cases, treatment with Xeed-4 tablets should be stopped immediately and the patient shall be evaluated for the following:

- Jaundice (associated with Isoniazid, Rifampicin and Pyrazinamide)
- Elevated liver enzymes associated with the clinical signs of hepatitis such as nausea and vomiting or fatigue.

Hepatic function determinations are based on ALT (SGPT) and AST (SGOT) concentrations i.e., serum alanine and aspartate aminotransferase concentrations. These tests may be required monthly during treatment, especially in the elderly, pregnant women and those with preliver damage.

Severe and sometimes fatal hepatitis has been reported.

- Rash and fever (associated with Isoniazid and Rifampicin)
- Bleeding tendency; shock; renal failure (associated with Rifampicin): Treatment to be discontinued permanently.
- Visual impairment (associated with Ethambutol)

**INTERACTIONS**

Rifampicin induces microsomal enzymes and may therefore accelerate clearance of medicines metabolised in the liver e.g., methadone; oral anticoagulants (coumarin derivatives); glucocorticoids, oestrogens; oral hypoglycaemic agents; digitoxin; antiarrhythmics (quinidine, verapamil, mexiletine); theophylline; anticonvulsants; beta-blockers;azole antifungals (ketonazole, fluconazole); cyclosporine.

Rifampicin enhances the metabolism of indinavir, thereby reducing its plasma concentration significantly. Hence its concomitant use should be avoided.

Isoniazid inhibits the hepatic drug metabolism of the following agents: Antiepileptics (e.g., phenytoin, primidone, carbamazepine, ethosuximide); benzodiazepines (e.g., diazepam); warfarin; theophylline.

Isoniazid may also increase the metabolism of some medicines e.g., enflurane. Other interactions: Alcohol (metabolism of isoniazid may be increased in chronic alcoholics); aminosalicylic acid; aluminium containing antacids (reduces oral absorption of isoniazid).

Pyrazinamide may decrease the efficacy of gout therapy (e.g., allopurinol, colchicine, probenecid or sulphipyrazone) and dosage adjustments of this medication may be necessary.

Concurrent administration of neurotoxic medication with Ethambutol may potentiate neurotoxic effects such as optic and peripheral neuritis.

**KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT**

Symptoms of Isoniazid overdose include slurred speech metabolic acidosis, hyperglycaemia, hallucinations, respiratory and CNS depression, convulsions and coma. Treatment of overdosage consists of gastric lavage symptomatic and supportive therapy. Haemodialysis may be of value in reducing serum concentrations of Isoniazid and Ethambutol.

**STORAGE INSTRUCTIONS**
Store at a temperature below 25°C, protect from light and moisture.
KEEP THE MEDICINE OUT OF REACH OF CHILDREN.

REFERENCES

1. Relative-bioavailability of rifampicin and isoniazid from Xeed-4 formulation (4 FDC wherein isoniazid is modified release) in comparison with reference conventional release formulation consisting of 4 individual drugs given as single dose in 24 adult male volunteers; (Data on file)