Summary of Product Characteristics

1. NAME OF MEDICINAL PRODUCT

REHEPTIN (Metadoxine, Silymarin, L-Ornithine L-Aspartate, Pyridoxine Hydrochloride & Folic Acid tablets.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REHEPTIN: Each film-coated tablet contains:

Metadoxine 500 mg,

Silymarin 140 mg,

L-Ornithine L-Aspartate 150 mg,

Pyridoxine Hydrochloride Ph. Eur 3mg,

Folic Acid Ph. Eur 1.5 mg.

Appropriate overages of vitamins are added.

For a full list of excipients, please refer to Section 6.1.

3. PHARMACEUTICAL FORMS

Film coated tablets

Pink coloured, Biconvex, elongated film coated tablets, plain on both sides

4. CLINICAL PARTIULARS

4.1 Therapeutic Indications

REHEPTIN tablets are indicated for the management of alcoholic & non-alcoholic fatty liver.

4.2 Dosage and Administration

One tablet twice a day or as directed by the physician

Mode of Administration: For oral use

4.3 Contraindications

Hypersensitivity to any of the ingredients present in **REHEPTIN**

4.4 Special warning and precautions for use

- Safety in children: Not recommended in children below 12 years of age
- Pregnancy & lactation: Not recommended in both the conditions due to the presence of Metadoxine.

4.5 Interaction with other medicinal products and other forms of interaction Metadoxine:

Metadoxine interacts with Levodopa and diminishes its effect. **Silymarin :**

- Cytochrome P450 2C9 (CYP2C9) substrates ,
- Glucuronidated drugs
- ***Tamoxifen*** - Silymarin might increase how much tamoxifen is absorbed

by the body.

- ***Silymarin*** along with estrogens might decrease the effectiveness of estrogen pills. Silymarin might change the levels of some medications used for lowering cholesterol (statins). This could increase or decrease how well these medications work.

L-Ornithine L-Aspartate*:* Drug interactions are not known

Pyridoxine :

- **Phenytoin:** Taking Pyridoxine and taking phenytoin might decrease the effectiveness of phenytoin and increase the possibility of seizure.
- **Amiodarone:** Taking Pyridoxine along with amiodarone might increase the chances of sunburn, blistering, or rashes on areas of skin exposed to sunlight.
- **Phenobarbital :** Pyridoxine might increase how quickly the body breaks down phenobarbital . This could decrease the effectiveness of Phenobarbital.
- **Levodopa :** Pyridoxine can increase how quickly the body breaks down and gets rid of levodopa. But this is only a problem if you are taking levodopa alone. Carbidopa prevents this interaction from occurring. If you are taking levodopa without carbidopa, do not take vitamin B6.

Folic Acid:

- Cimetidine and antacids appear to reduce folate absorption.
- Sulfasalazine interferes with folic acid absorption and conversion to the active form.
- Anti-seizure medications, including carbamazepine and phenobarbital, appear to utilize folic acid during hepatic metabolism.
- The anticonvulsant drugs phenytoin and valproic acid appear to interfere with folate absorption

4.6 Pregnancy & Lactation

Pregnancy: Not recommended in pregnant females due to presence of Metadoxine. Lactation: Not recommended in lactating females due to presence of Metadoxine.

4.7 Undesirable effects

Metadoxine: No side-effects or unfavorable reactions occurred during Metadoxine treatment.

Silymarin: Silymarin is has a good safety record and only rare case reports of gastrointestinal disturbances and allergic skin rashes have been reported. Occasional laxative effects. Abdominal bloating, diarrhoea, flatulence, loss of appetite, anorexia, nausea, stomach upset.

L-Ornithine L-Aspartate : No side effects are known

Pyridoxine : Sensory neuropathic syndromes , unstable gait, numb feet, awkwardness of hands, perioral numbness, decreased sensation to touch, temperature & vibrations, paresthesia, photoallergic reactions, ataxia.

Folic Acid: Anorexia, Nausea, abdominal distension.

4.8 Overdose

Folic acid: Fever, weakness, wheezing, rashes

Silymarin: Hepatic disorders

Metadoxine: Neuropathy

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties Metadoxine

Metadoxine is the ion-pair between pyridoxine and pyrrolidone carboxylate. Both substances have been used in the treatment of alcoholic liver disease. Pyridoxine is metabolized in the liver and released to systemic circulation principally as pyridoxal-P. It increases the clearance of alcohol and acetaldehyde and decreases the damaging effect of free radicals, restores ATP and glutathione levels, reduces steatosis and liver fibrosis. Metadoxine reduces the toxic effects of alcohol. In hepatic stellate cells, Metadoxine prevents the collagen synthesis & reduces fibrosis and acts as an Antifibrotic agent and is a synthetic antioxidant, provides stronger antioxidant protection.Besides of its effect on hepatic enzyme systems with subsequent acceleration of ethanol metabolism. Metadoxine is therefore an antagonist of alcohol-metabolic effects.

Silymarin

Silymarin, a flavanoid from the seeds of 'milk thistle' *(Silybum marianum),* has been widely used from ancient times because of its excellent hepatoprotective action. It is a mixture of mainly three flavonolignans, viz, silybin, silidianin, and silychristine, with silybin being the most active. Silymarin has been used medicinally to treat liver disorders, including acute and chronic viral hepatitis, toxin/drug-induced hepatitis, and cirrhosis and alcoholic liver diseases. It has also been reported to be effective in certain cancers. Its mechanism of action includes reduction of glutathione oxidation to enhance its level in the liver and intestine; antioxidant activity; and stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration.

Silymarin has metabolic and cell-regulating effects at concentrations found in clinical conditions, namely carrier-mediated regulation of cell membrane permeability, inhibition of the 5-lipoxygenase pathway, scavenging of reactive oxygen species (ROS) of the R-OH type and action on DNA-expression.

L-Ornithine L-Aspartate

L-ornithine-L-aspartate (LOLA), the stable salt of the amino acids ornithine and aspartic acid, in several clinical trials has shown to reduce blood ammonia levels and improve psychometric performance in patients with HE. LOLA stimulates the urea cycle and glutamine synthesis, which are important mechanisms in ammonia detoxification. Over the last two decades, studies involving use of L-ornithine aspartate in patients with liver cirrhosis have demonstrated beneficial effects. Proposed mechanisms as basis for the use of "ammonia lowering" drugs, particularly amino acids, such ornithine-aspartate include the following:

- in cirrhotic patients, aspartate and citric dicarboxylates may serve as carbon sources for impaired glutamine synthetase flux in the perivenous scavenger hepatocytes; and
- ornithine improves the flux through the impaired urea cycle enzyme system, especially through carbamylphosphate synthetase, localized in the periportal hepatocytes.

Pyridoxine

A deficiency of vitamin B6 has been shown to result in impaired hepatic incorporation of titrated thymidine in vitro and, because of this, hepatic regeneration may be adversely affected. Furthermore, PLP plays an important role in the metabolism of amino acids , whose disordered homeostasis may be important in the pathogenesis of hepatic encephalopathy. Subnormal levels of PLP may well exacerbate abnormalities, as well as leading to impaired utilisation of dietary protein. Supplementation with vitamin B6 should therefore be included in the nutritional management of patients· Deficiency of pyridoxine interfere with metabolism & decrease the availability of ATP needed for protein synthesis. Protein deficiency in general may cause fatty liver·

Folic Acid

Liver injury induced chemically can be experimentally used to mimic many types of liver disease. Folate is being utilized to treat a wide variety of disease like hepatotoxicity via., selective cellular markers can reduce the toxicity of therapeutics agents. Oxidative stress plays a major role in several liver diseases. Study show that folate supplementation regimens reduce the incidence of elevated lever enzyme levels by acting as an anti oxidant

5.2 Pharmacokinetic

properties Metadoxine

Metadoxine is readily absorbed after oral administration. It is primarily stored in liver & to a lesser extent in muscles & brain. Metadoxine is metabolized in the liver & excreted in urine.

Silymarin

Silymarin is an active principle from the fruit of *Silybum marianum*, which contains a mixture of flavonolignans. It reduces the turnover of membrane phospholipids and stabilises the cell membranes of hepatocytes. It has potent

antioxidant action and prevents lipid peroxidation. Absorption of Silymarin after oral administration is low & peak plasma concentrations are achieved in 4 to 6 hours. Silymarin is distributed into the digestive tract (liver, stomach, intestine & pancreas) and is metabolized via liver. It is mainly excreted in the bile and to a lesser degree in the urine.

L-Ornithine L-Aspartate

Absorption of L-Ornithine L-Aspartate happens in small intestine. It is distributed throughout the body & metabolized via liver & excreted via urine & faeces

Pyridoxine

Pyridoxine is absorbed into the upper small intestine. It is readily absorbed from the gastrointestinal tract, except in malabsorption syndromes and mainly absorbed in the jejunum. Pyridoxine metabolized via liver & excreted via urine

Folic Acid

Approx, 70-80% of Folic acid is absorbed and is distributed in the tissues throughout the body & metabolized via liver. The primary methods of elimination of absorbed folic acid are through faeces and urine.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose, Croscarmellose sodium, Hydroxypropylmethyl cellulose, Colloidal Silicon dioxide, Magnesium stearate, Isopropyl alcohol, Purified Talc, Opadry Pink 200F 540051 (Polyvinylalcohol, Titanium dioxide, Polyethylene Glycol, Purified Talc, Methacrylic acid copolymers, Sodium bicarbonate), Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

24 months from the date of manufacture.

6.4 Special Precautions for Storage

Store below 30° C. Protect from light and moisture Keep out of the reach & sight of children.

6.5 Nature and Contents of Container

REHEPTIN: 10 Tablets packed Alu/Alu blister. One such blister is packed in a carton along with a package insert.

6.6 Special Precautions for Disposal

No special requirements.

7. Marketing Authorization Holder

Mankind Pharma Ltd.
Unit-II, Village-Kishanpura, P.O.
Jamniwala Tehsil- Paonta Sahib,
District Sirmour- 173 025, Himachal
Pradesh (India)

Regd. Office: 208, Okhla Industrial
Estate, Phase-3 New Delhi-110020 (INDIA)

8. Marketing Authorization Number

H2022/CTD7642/14540

9. Date of first authorization/renewal of the authorization

09/10/2023

10. Date of revision of the text

09/10/2023