

Summary of Product Characteristics

Merz Pharmaceuticals GmbH

Hepa-Merz granules

1. NAME OF THE MEDICINAL PRODUCT

Hepa-Merz granules, 3 g
Granules for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: L-ornithine-L-aspartate.
Each sachet with 5 g contains 3 g L-ornithine-L-aspartate.

Excipients: yellow orange S (E 110), fructose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral solution.

The granules are orange in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of concomitant disease and sequelae due to impaired hepatic detoxification activity (e.g. in cirrhosis of the liver) with the symptoms of latent and manifest hepatic encephalopathy.

4.2 Posology and method of administration

The dissolved contents of 1-2 sachets of Hepa-Merz granules are taken up to 3 times daily.
Hepa-Merz granules are dissolved in plenty of fluid (e.g. a glass of water, tea or juice) and taken with or after meals.

The experiences on the use of the drug in children are limited (see chapter 4.4).

4.3 Contraindications

Hypersensitivity to L-ornithine-L-aspartate, orange yellow S or any of the excipients.

Severely impaired renal function (renal insufficiency). A serum creatinine value over 3 mg / 100 ml can be used as a guideline value.

4.4 Special warnings and special precautions for use

Hepa-Merz Granules contain fructose. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Hepa-Merz granules contain 1.13 g fructose per sachet (equivalent to 0.11 CEU). This should be taken into account in patients with diabetes mellitus.

Hepa-Merz granules may be harmful to the teeth (caries) in long-term use.

No data are so far available on the use of the drug in children.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Up to now interactions are not known.

4.6 Pregnancy and lactation

No clinical data are available relating to intake of Hepa-Merz granules during pregnancy. No exhaustive animal studies have been performed for L-ornithine-L-aspartate, to investigate its toxicity in relation to reproduction. Administration of Hepa-Merz granules during pregnancy should therefore be avoided. If, however, treatment with Hepa-Merz granules is considered necessary, careful consideration should be given to the benefit versus risk ratio.

It is not known whether L-ornithine-L-aspartate is excreted into the breast milk. Administration of Hepa-Merz granules should therefore be avoided during lactation. If, however, treatment with Hepa-Merz granules is considered necessary, careful consideration should be given to the benefit versus risk ratio.

4.7 Effects on ability to drive and use machines

As a result of the disease, the ability to drive and use machines may be impaired during treatment with L-ornithine-L-aspartate.

4.8 Undesirable effects

Very common:	(>1/10)
Common:	(>1/100, <1/10)
Uncommon:	(>1/1000, <1/100)
Rare:	(>1/10000, <1/1000)
Very rare:	(<1/10000), not known (cannot be estimated from the available data)

Gastrointestinal disorders

Uncommon: Nausea, vomiting, stomach ache, flatulence, diarrhoea.

Musculoskeletal and connective tissue disorders

Very rare: pain in the limbs

These undesirable effects are usually transient and do not require withdrawal of the medicine.

Orange yellow S (E 110) can trigger allergic reactions.

4.9 Overdose

So far signs of intoxication have not been observed following an overdose of L-ornithine L-aspartate. Symptomatic treatment is recommended if overdose occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Liver therapy, *ATC code:* A05BA

In vivo, L-ornithine-L-aspartate exerts its effects through the amino acids, ornithine and aspartate, via two key methods of ammonia detoxification: urea synthesis and glutamine synthesis.

Urea synthesis takes place in the periportal hepatocytes. In these cells, ornithine serves both as an activator of the enzymes ornithine-carbamoyltransferase and carbamoyl phosphate synthetase and also as the substrate of urea synthesis.

Glutamine synthesis is localised in the perivenous hepatocytes. Particularly under pathological conditions, aspartate and other dicarboxylates, including the metabolic products of ornithine, are absorbed into the cells and used there to bind ammonia in the form of glutamine.

Glutamate is an amino acid that binds ammonia under both physiological and pathophysiological conditions. The resulting amino acid glutamine not only represents a non-toxic form for the excretion of ammonia, but also activates the important urea cycle (intercellular glutamine exchange).

Under physiological conditions, ornithine and aspartate are not limiting for urea synthesis.

Animal studies suggest that the ammonia-reducing effect of L-ornithine-L-aspartate is caused by enhanced glutamine synthesis. Individual clinical studies have shown an improved branched-chain amino acid/aromatic amino acid quotient.

5.2 Pharmacokinetic properties

L-ornithine-L-aspartate is rapidly absorbed and cleaved to form ornithine and aspartate. Both amino acids have a short elimination half-life of 0.3 – 0.4 hours. A fraction of the aspartate is recovered in unmetabolised form in the urine.

5.3 Preclinical safety data

Preclinical data, based on safety pharmacological studies and chronic toxicity and mutagenicity studies, do not suggest any particular risk to humans following correct administration.

No studies into any carcinogenic potential have been performed.

In a dose-finding study, L-ornithine-L-aspartate was insufficiently investigated in terms of its toxicity in relation to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid,
saccharin sodium,
sodium cyclamate,
povidone 25,
fructose,
flavourings,
orange yellow S (E 110).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Original packs are available containing 10, 30, 50, 100 and 250 sachets of granules for oral solution.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH
Eckenheimer Landstr. 100
60318 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]