Summary of Product Characteristics

Merz Pharmaceuticals GmbH **Hepa-Merz infusion concentrate**

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1. NAME OF THE MEDICINAL PRODUCT

Hepa-Merz infusion concentrate, 5g/ampoule
Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: L-ornithine L-aspartate.
One ampoule of 10 ml contains 5 g L-ornithine-L-aspartate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Hepa-Merz infusion concentrate is a clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Latent and manifest hepatic encephalopathy.

4.2 Posology and method of administration

Unless otherwise indicated, patients may be given up to 4 ampoules per day.

With incipient clouding of consciousness (precoma) or clouding of consciousness (coma), up to 8 ampoules may be given in 24 hours, depending on the severity of the condition.

The ampoules are added to an infusion solution before use, and infused in this form.

Hepa-Merz infusion concentrate can be mixed with the usual infusion solutions without any problem. For venous tolerability, however, no more than 6 ampoules should be dissolved per 500 ml infusion.

The maximum infusion rate is 5 g L-ornithine L-aspartate (corresponding to the content of 1 ampoule) per hour.

Hepa-Merz infusion concentrate must not be administered into an artery.

Experience in children is limited (see section 4.4).

4.3 Contraindications

Hypersensitivity to L-ornithine L-aspartate.

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

4.4 Special warnings and precautions for use

At high doses of Hepa-Merz infusion concentrate, serum and urine urea levels should be monitored.

If liver function is substantially impaired, the infusion rate must be adjusted to the individual patient in order to prevent nausea and vomiting.

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

There are no clinical data available on the use of Hepa-Merz infusion concentrate in pregnancy.
L-ornithine L-aspartate has been investigated for reproduction toxicity only to a limited extent in experimental animal studies. The administration of Hepa-Merz infusion concentrate in pregnancy should therefore be avoided. If treatment with Hepa-Merz is nevertheless thought to be necessary, the benefits and risks should be carefully assessed.

It is not known whether L-ornithine L-aspartate passes into breast milk. Administration of Hepa-Merz should therefore be avoided during lactation. If treatment with Hepa-Merz is nevertheless thought to be necessary, the benefits and risks should be carefully assessed.

4.7 Effects on ability to drive and use machines

Depending on the underlying disease, the ability to drive and operate machines may also be impaired on 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
Rare: Vomiting
Generally, however, these symptoms are transient, and do not necessitate discontinuation of treatment with this medicinal product. They disappear on reduction of the dose or infusion rate.

4.9 Overdose

So far signs of intoxication have not been observed following an overdose of L-ornithine L-aspartate. Cases of overdose require symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

In vivo, L-ornithine L-aspartate acts on two key ammonia detoxification pathways – urea synthesis and glutamine synthesis – via the amino acids ornithine and aspartate.

Urea synthesis takes place in the periportal hepatocytes, in which ornithine serves both as an activator of the two enzymes ornithine carbamoyl transferase and carbamoyl phosphate synthetase and as a substrate for urea synthesis.

Glutamine synthesis is localised in the perivenous hepatocytes. Under pathological conditions in particular, aspartate and other dicarboxylates – including metabolic products of ornithine – are taken up into the cells where they are used in the form of glutamine to bind ammonia.

Both physiologically and pathophysiologically glutamate serves as an ammonia-binding amino acid. The resulting amino acid glutamine not only provides 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.

Experimental studies in animals point to increased glutamine synthesis as a mechanism of the ammonia-lowering effect. Some clinical studies have shown an improvement in the ratio of branched-chain to aromatic amino acids.

5.2 Pharmacokinetic properties

Ornithine and aspartate have a short elimination half-life of 0.3–0.4 hours. Some of the aspartate is excreted unchanged in the urine.

5.3 Preclinical safety data

Based on pharmacological safety studies, preclinical data show that with correct use there is no particular risk of toxicity following repeated administration or mutagenicity in humans.

No studies on carcinogenic potential have been carried out.

In a dose discovery study, L-ornithine L-aspartate was investigated for reproduction toxicity only to a limited extent.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

As no compatibility studies have been performed the medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

The concentrate to be made up into solution for infusion is presented in amber-coloured glass ampoules.
Original packs containing 5, 10, 25 and 30 ampoules of 10 ml infusion concentrate.
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.]