SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
HEPALORNITIN 5 g / 10 ml I.V. concentrate for solution for infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substance:
Each vial (10 ml) contains 5 g of L-ornithine L-aspartate.

Excipients:
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Sterile concentrate for solution for intravenous infusion
Clear solution

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is used to treat latent and prominent hepatic encephalopathy.

4.2 Posology and method of administration
Posology / frequency and duration of application:
If not otherwise recommended by the doctor, it is administered a maximum of 4 vials per day. Depending on the severity of the patient's condition, 8 vials may be given within 24 hours in the case of newly started confusion (precoma) or brain fog (coma).

The maximal infusion rate of L-ornithine-L-aspartate is 5 g per hour (equivalent to the contents of a vial).

Method of Application:
The contents of the vial are added to the infusion solution and this is given to the patient. HEPALORNITIN can be easily mixed into normally used infusion solutions. Considering the venous capacity, the infusion volume is adjusted. The HEPALORNITIN infusion concentrate should not be administered into the artery.

Additional information on special populations:
Renal / Hepatic failure:
It should not be used in case of severe renal failure. The serum creatinine value is used as the reference value. In cases where serum creatinine is below 3 mg/100 ml or less, HEPALORNITIN is continued. HEPALORNITIN should not be used if this value is greater than 3 mg/100 ml.

If there is damage at the liver functioning, the infusion rate should be adjusted depending on the patient's condition. In this way, nausea and vomiting can be prevented.
Pediatric population:
Experience in children is limited.

Geriatric population:
There is no specific information on its use in the elderly population.

4.3. Contraindications
It is contraindicated in those sensitive to L-ornithine L-aspartate.
It is contraindicated in patients with severe kidney function impairment (renal failure) (as a reference value, serum creatinine value being more than 3 mg / 100 ml can be used).

4.4 Special warnings and precautions for use
When HEPALORNITIN is used in high doses, urea level should be monitored in serum and urine.

If liver function is severely damaged, your doctor will adjust the infusion rate to prevent nausea and vomiting.

4.5 Interaction with other medicinal products and other forms of interaction
There is no known interaction study.

Additional information on special populations:
There is no interaction study for special populations.

Pediatric population:
There is no interaction study on pediatric populations.

4.6 Pregnancy and lactation
General recommendation
Pregnancy Category: B.

Women with childbearing potential / Contraception
There are no studies on contraception.

Pregnancy
Animal studies do not show any direct or indirect adverse effects on pregnancy / embryonal / fetal development / birth or postnatal development.

There is no clinical data on exposure to HEPALORNITIN during pregnancy. L-ornithine L-aspartate has been shown to cause a low level of reproductive toxicity. Therefore, the use of HEPALORNITIN concentrated infusion solution should be avoided during pregnancy. However, if treatment with HEPALORNITIN is considered necessary, the potential benefits and damages should be carefully evaluated.

Lactation
It is not known whether L-ornithine L-aspartate is excreted in human milk. The excretion of L-ornithine L-aspartate with milk has not been studied on animals. When deciding whether to stop breastfeeding or whether treatment with HEPALORNITINE should be stopped, the
benefit of breastfeeding for the child and the benefit of HEPALORNITIN treatment for breastfeeding mother should be taken into consideration.

Fertility
There are no controlled studies on the effect of L-ornithine L-aspartate on reproductive ability.

4.7 Effects on ability to drive and use machines
HEPALORNITIN has no direct, negative effect on ability to drive and use machine. However, in patients treated with L-ornithine L-aspartate, depending on the disease, the ability to drive and use machines may decrease. Therefore, it is recommended that patients avoid using tools and machines until recovery.

4.8 Undesirable effects
The frequency of adverse reactions is listed as follows:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Immune system disorders
Not known: Hypersensitivity reactions, anaphylactic reactions

Gastrointestinal disorders
Uncommon: Nausea
Rare: Vomiting
Nausea and vomiting are mild side effects of HEPALORNITIN. These effects are usually temporary and do not require discontinuation of treatment. This is eliminated by reducing the dose or lowering the infusion rate.

Reporting of suspected adverse reactions
Reporting any suspected adverse reactions of drugs is very important after the authorization. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0312 218 35 99).

4.9. Overdose and therapy
Up to the present, no evidence of intoxication due to overdose of L-ornithine L-aspartate has been reported. Cases of overdose require symptomatic treatment.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in liver diseases
ATC code: A05BA

Mechanism of action:

In vivo, L-ornithine L-aspartate shows the effect via ornithine and aspartate amino acids, through the synthesis of urea and glutamine synthesis which is two basic ammonia detoxification pathways,

Urogenesis takes place in periportal hepatocytes, where ornithine acts both as activator of carbamyl transferase and carbamyl phosphate synthetase enzymes as well as as substrate for urea synthesis.

Glutamine Synthesis occurs in perivenous hepatocytes. Other dicarboxylates, including the metabolic products of aspartate and ornithine, are taken into the cells and used in ammonia binding by converting them to the form of glutamine.

Under physiological and pathophysiological conditions, glutamate acts as an ammonia-binding amino acid. The resulting glutamine amino acid not only allows the removal of ammonia in non-toxic form, but also activates the urea cycle (intercellular glutamine exchange). Under physiological conditions, ornithine and aspartate are not limiting factors for urea synthesis.

Experimental studies in animals have shown that the increase in glutamine synthesis is a mechanism to reduce the level of ammonia. Some clinical trials have shown improvement in the ratio of branched-chain amino acids changing to aromatic amino acids.

5.2 Pharmacokinetic properties

General properties:
L-ornithine-L-aspartate is rapidly separated into L-ornithine and L-aspartate amino acids, which are rapidly metabolized. Pharmacokinetic evaluations are mainly related to ornithine.

Absorption:
Following intravenous administration, ornithine is reached to the maximum plasma concentration ($C_{\text{max}}$) determined as $897 \pm 328 \ \mu\text{mol/L}$ at $0.55 \pm 0.16$ hours. The endogenous ornithine level is reached after 7 hours of intravenous infusion.

Distribution:
The terminal half-life ($t_{1/2}$) for L-ornithine and L-aspartate were $4.5 \pm 1.3$ hours and $5.3 \pm 2.8$ hours, respectively, and the distribution volumes were $9.1 \pm 3.7 \ \text{L}$ and $8.8 \pm 3.7 \ \text{L}$ respectively.

Biotransformation:
There is no information available.

Elimination:
After the infusion, a biphasic condition is observed and in the first stage of this phase the rapid dispersion phase is $t_{1/2} = 15-25$ min, while in the second stage slower final elimination phase is $t_{1/2} = 120-150$ min. After intravenous administration, the area under the plasma
concentration time (AUC$_{0-7h}$) curve for ornithine is 1390 ± 160 µmol.hour/L. A portion of the aspartate is excreted in the urine without transformation.

5.3 Preclinical safety data
Preclinical data from pharmacological safety studies did not reveal any risk of toxicity or mutagenicity in humans after repeated doses, if it is used correctly.
No studies have been conducted regarding the carcinogenic potential.
In the dosing study, the reproductive toxicity of L-ornithine-L-aspartate has been shown to be quite low.

6. PHARMACEUTICAL PROPERTIES
6.1 List of Excipients
Water for Injection

6.2 Incompatibilities
It should not be used with other medicinal products since there is no study for incompatibility.
No other active substance should be added to the infusion solution. In conditions such as precipitation, opacification that indicate degradation in resolution, it should not be used.

6.3 Shelf life
24 month.

6.4 Special precautions for storage
Store at room temperature below 25 °C.

6.5 Nature and contents of container
10 pieces in a box; Type 1 amber colored glass vial.

6.6 Special precautions for disposal and other handling
Unused products or waste materials must be disposed of in accordance with the “Medical Waste Control Regulations” and “Packaging and Packaging Waste Control Regulations”.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER
2019/8

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 10.01.2019
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT
27.12.2019