**SUMMARY OF PRODUCT CHARACTERISTICS**

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## 1. NAME OF THE MEDICINAL PRODUCT

Legalon ® SIL 528.5 mg (equivalent to 350 mg silibinin) powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: silibinin-C-2',3-dihydrogen succinate, disodium salt

1 vial of 598.5 mg powder for solution for infusion contains:
Active pharmaceutical ingredient:
528.5 mg silibinin-C-2´,3-dihydrogen succinate, disodium salt
[corresponding to 476 mg mono-, dihydrogensuccinate sodium salts (HPLC)]
equivalent to 350 mg (315 mg HPLC) of silibinin

After reconstitution with 35 ml solution for infusion, 1 ml contains 10 mg (9 mg HPLC) silibinin.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion

The powder is a beige-coloured microcrystalline lyophilisate.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Hepatic intoxication by Amanita phalloides.

### 4.2 Posology and method of administration

Posology

The recommended daily dosage amounts to 20 mg silibinin per kg body weight distributed over 4 infusions, each of 2 hours duration, and taking into account the fluid balance. Accordingly, 5 mg silibinin per kg body weight are administered per infusion.

In the case of a patient weighing 70 kg, for example, the contents of one rubber-stoppered vial (≙ 350 mg silibinin) is required for one infusion. Repeat the infusions at 4-hour intervals so that a total of 4 infusions are administered every 24 hours.

The administration of Legalon SIL infusions should be initiated as early as possible after intoxication, even if the final diagnosis of fungus poisoning is still not certain.

The infusions should be continued over several days until the symptoms of intoxication have disappeared (refer also to section 4.4).

Method of administration

Administration is carried out via intravenous infusion.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Extracorporeal detoxication measures such as hemoperfusion and hemodialysis should be started in the intervals between the infusions, in order to minimize as much as possible the removal of silibinin from the circulation.
A rigorous control of the electrolyte and acid-base metabolism and also of the fluid balance must be carried out in the patients. Approx. 0.36 mmol sodium per kg body weight are supplied with the recommended daily dose of 20 mg silibinin per kg body weight and the corresponding amount of sodium chloride used to dissolve it.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

## 4.6 Fertility, pregnancy and lactation

For silibinin-C-2´,3-dihydrogen succinate, disodium salt there are no adequate data from the use in pregnant and breast-feeding women. Investigations on animals did not reveal a direct or indirect effect on pregnancy, embryo or fetal development, birth or postnatal development (see section 5.3).
Administration during pregnancy with caution.

Data on the effects of silibinin-C-2´,3-dihydrogen succinate, disodium salt on fertility are not available.

## 4.7 Effects on ability to drive and use machines

Not relevant.

## 4.8 Undesirable effects

The data on undesirable effects are based on the following categories:

| | |
|---|---|
| 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 |

General disorders and administration site conditions
Heat sensation (flush) during infusion (very rare), fever (frequency not known).

Investigations
Blood bilirubin increased (frequency not known)

## 4.9 Overdose

No cases of overdose have been reported.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote.
ATC-code: V03AX

The antitoxic mechanism of action of silibinin in the case of deathcap fungus poisoning is based on an inhibition of the uptake of amatoxins in the liver cells and thus an interruption of the enterohepatic circulation of amatoxins. Hence the actual intracellular concentration of amatoxins and thus their toxicity is reduced. At the same time, biliary elimination remains uninfluenced.

An increase in the liver cells´ capacity for synthesis is caused by a stimulation of the formation of ribosomal RNA. The result is an unspecific increased formation of all cellular synthesis products.

## 5.2 Pharmacokinetic properties

During an infusion of Legalon SIL of 2 hours´ duration silibinin ester is only detectable in the plasma in unconjugated form. Elimination from the blood takes place so rapidly that only small amounts of conjugated silibinin-C-2´,3-dihydrogen succinate, disodium salt are detectable, three hours after the end of infusion. After esterification silibinin is also detectable. From the blood analyses it may be assumed that silibinin-C-2´,3-dihydrogen succinate, disodium salt is rapidly eliminated and metabolised. Therefore, the intervals between infusions should not exceed 3 – 4 hours and an intravenous drip appears to be the most suitable form of administration.

## 5.3 Preclinical safety data

In the acute test silibinin-C-2´,3-dihydrogen succinate, disodium salt proved to be practically non-toxic. The $LD_{50}$ values after intravenous injection may thus be accepted for rats and mice of both sexes as > 1000 mg/kg.

After intravenous, intraarterial or intramuscular injection a good local tolerance was observed in rats and rabbits.

In a subacute study over 4 weeks, the active ingredient was well tolerated by male and female beagle hounds in the dose range investigated up to 150 mg/kg per infusion – except for a low-grade transient depressant effect on the circulation in the high dosage group.

Toxicological investigations into the reproduction of rats and rabbits did not reveal any embryo-lethal and/or teratogenic effects after doses of up to 50 mg/kg. After the administration of higher doses, fetal death due to maternal toxic effects was recorded.

Mutagenicity tests carried out on microorganisms (Ames Test) and mammalian cells in vitro (CHO- and Mouse-Lymphoma Test) were all negative.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Inulin

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

5 years

The chemical and physical stability of this ready-to-use preparation has been demonstrated for a period of 6 hours at 30 °C and 24 hours at 2 - 8 °C. From the microbiological point of view the ready-to-use preparation should be used immediately, the user will be responsible for the duration and conditions of storage.

## 6.4 Special precautions for storage

Do not store above 25 °C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Vial of amber glass with a butyl rubber stopper and an aluminium crimp cap with polypropylene flip-off cap.

One package contains: 4 vials containing each 598.5 mg powder for solution for infusion.

## 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

The contents of the rubber-stoppered vial are dissolved in 35 ml infusion (e.g. 5 % glucose or 0.9 % sodium chloride solution) (1 ml ≅ 10 mg silibinin) and added to the infusion.

The reconstituted medicinal product is a clear, light yellow solution.

# 7. MARKETING AUTHORIZATION HOLDER

(Germany)
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# 8. MARKETING AUTHORIZATION NUMBER

4178.00.00 (Germany)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORIZATION

Date of first authorisation (Germany):18 April 1984
Date of latest renewal (Germany): 17 January 2005

## 10. DATE OF REVISION OF THE TEXT

July 2015

## 11. LEGAL CATEGORY

Prescription only medicine