

Antidotum Thallii-Heyl[®]



1. NAME OF THE MEDICINAL PRODUCT

Antidotum Thallii-Heyl[®]

500 mg hard capsules

Active pharmaceutical ingredient: Ferric hexacyanoferrate(II)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 hard capsule contains 500 mg ferric hexacyanoferrate(II) (68 % $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$) (Prussian blue insoluble).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Thallium poisoning

4.2 Posology and method of administration

The dosage depends on the severity of the intoxication with thallium.

Dosage for adults, children over 2 years and adolescents:

- If absorption of thallium has already taken place, and for chronic thallium intoxication 6 to 40 hard capsules of Antidotum Thallii-Heyl [3 to 20 g ferric hexacyanoferrate(II)] orally each day. The daily dose should be distributed evenly over the 24-hour period (e.g. 3 x 6 hard capsules daily) in order to interrupt the enterohepatic circulation of the thallium optimally.
- In cases of acute intoxication, where the thallium is still present in the stomach or upper parts of the intestinal tract, an initial dose of at least 6 hard capsules [3 g ferric hexacyanoferrate(II)] should be taken in one dose.

Methods of administration

The hard capsules should be taken with liquid.

Patients, who cannot swallow the capsules, may open them. The ingredient may be taken mixed with food or be drunk dispersed in fluid (e.g. in warm water). This may result in blue discoloration of the mouth and teeth.

The administration of the suspension can also follow gastric lavage via stomach intubation.

If oral intake is not possible, the content of the hard capsules can be suspended in water or a mannitol solution and administered by stomach or duodenal intubation.

The hard capsules should be taken during mealtimes, since food stimulates bile secretion and the enterohepatic circulation (possible stimulation of thallium excretion).

Treatment with Antidotum Thallii-Heyl should be initiated as soon as possible. If Antidotum Thallii-Heyl is not available immediately, treatment is still effective and reasonable even after time has elapsed since exposure.

The duration of treatment is dictated by the detection of thallium in the faeces.

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

None known so far.

4.5 Interactions with other medicinal products and other forms of interaction

Antidotum Thallii-Heyl may bind to other oral administered drugs and essential nutrients. Therefore the drug levels and the clinical response to the therapy should be monitored.

Antidotum Thallii-Heyl may inhibit the absorption of tetracyclines.

Antidotum Thallii-Heyl may bind electrolytes in the gastrointestinal tract (e.g. potassium), which can result in lowered potassium levels in serum (asymptomatic hypokalemia). Therefore serum electrolytes should be regularly monitored during the therapy. Special caution should be exercised when treating patients with pre-existing cardiac arrhythmias or electrolyte imbalances.

In cases of poisoning with radioactive thallium the co-administration of other radioeliminators does not affect the efficacy of Antidotum Thallii-Heyl for thallium.

4.6 Fertility, pregnancy and lactation

There are no reservations against use during pregnancy and breast-feeding.

Since Antidotum Thallii-Heyl is practically not absorbed from the gastrointestinal tract, it does not pass the placental barrier and is not excreted into breast milk. However thallium is transmitted both to the fetus and into breast milk. Therefore the risk of thallium is expected to be greater than the risk of treatment with Antidotum Thallii-Heyl.

Thallium contaminated mothers should not breast feed in general.

4.7 Effects on ability to drive and use machines

None known so far.

4.8 Undesirable effects

Gastrointestinal disorders

The intake of Antidotum Thallii-Heyl can cause constipation. This may be treated with a high fiber diet or fiber based laxatives.

In high dosage (20 g ferric hexacyanoferrate(II) daily) undefined gastric distress may occur.

Note: Dark coloration of the faeces is harmless; it is due to the color of the active ingredient ferric hexacyanoferrate(II) [Prussian blue insoluble].

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 asked to report any suspected adverse reactions to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose

No case of overdose of Antidotum Thallii-Heyl has been reported.

Symptoms of overdose may be constipation, obstruction, or severe decrease in electrolytes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidote

ATC-Code: V03AB31 ferric hexacyanoferrate(II)

Thallium is subject to enterohepatic circulation. During this process, thallium reaches the intestines via the liver and the gallbladder. There, partial reabsorption through the intestinal mucosa takes place, which results in a renewed intoxication.

Ferric hexacyanoferrate(II) (Prussian blue insoluble) is practically not absorbed by intact mucosa after oral administration. It binds monovalent cations, where the strength of binding rises with increasing ionic radius: $\text{Na}^+ < \text{K}^+ < \text{NH}_4^+ < \text{Rb}^+ < \text{Tl}^+ < \text{Cs}^+$.

Prussian blue insoluble binds the thallium in the intestines and prevents its absorption or reabsorption. So the enterohepatic circulation will be interrupted. The thallium is excreted in the faeces together with the antidote. By the enhanced fecal excretion the dwell-time of the thallium in the organism is diminished and thus its toxicity is reduced.

Due to the decreased excretion of thallium in the bile Antidotum Thallii-Heyl may be less effective in patients with impaired liver function (However its use is not contraindicated in this group of patients).

Prussian blue insoluble reduces the biological half-life of thallium from 8 days to approximately 3 days.

5.2 Pharmacokinetic properties

The solubility product of Prussian blue is extremely small and it is practically not absorbed after oral administration. Thus it is not subject to pharmacokinetics in its proper meaning.

5.3 Preclinical safety data

Studies with Prussian blue insoluble to evaluate carcinogenesis, mutagenesis and impairment of fertility have not been performed. Since the active ingredient is not absorbed, no effects are expected.

a) Acute toxicity

Overdoses and intoxications by ferric hexacyanoferrate(II) are so far unknown (See "4.9 Overdose"). The LD_{50} in rats via oral administration is > 10 g/kg of body weight, for long term application > 1 g/kg of bodyweight.

b) Chronic toxicity / subchronic toxicity

Ferric hexacyanoferrate(II) is not metabolized in the intestines. The long term administration of 1 % Prussian blue in the feed does not give rise to pathological alterations in rats.

c) Mutagenic and carcinogenic potential

Studies with Prussian blue to assess the carcinogenicity and mutagenicity have not been performed. Since the active ingredient is not absorbed, no effects are expected.

d) Reproductive toxicity

Studies with Prussian blue to assess the reproductive toxicity have not been performed. Since the active ingredient is not absorbed, no effects are expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, gelatin, indigo carmine (E132), sodium dodecylsulfate, water for injection.

6.2 Incompatibilities

None known so far.

6.3 Shelf life

The shelf life is five years.

The expiry date of this medicinal product is printed on the label and on the carton.

6.4 Special precautions for storage

Keep out of the reach and sight of children!

Do not store above 25 °C!

6.5 Nature and contents of container

Antidotum Thallii-Heyl is available in a jar with 30 blue hard capsules.

6.6 Special precautions for disposal and other notes

No special requirements for disposal.

In cases of acute thallium intoxication supportive treatment such as forced vomiting, gastric lavage or hemodialysis can be necessary.

Thallium is excreted in the urine and faeces. In cases of poisoning with radioactive thallium appropriate safety measures should be taken to avoid contamination of other persons.

Please note that the content of the hard capsules has a strong coloration effect (Prussian blue insoluble).

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

6813022.00.00

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24.09.1997

Date of the latest renewal of the authorisation: 08.07.2009

10. DATE OF REVISION OF THE TEXT
March 2015

11. PRESCRIPTION STATE
By prescription only