HUMATIN® Capsules

1. NAME OF THE MEDICINAL PRODUCT (S)
Humatin® Capsules, hard capsules
250 mg
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance : Paromomycin
Each hard capsule contains 357.1 mg paromomycin sulfate corresponding to 250 mg paromomycin
For a full list of excipients, see **section 6.1**.
3. PHARMACEUTICAL FORM
Hard capsule
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Humatin Capsules are indicated in the following conditions in adults :
- Therapy and prophylaxis of portosystemic encephalopathy
- Preoperative reduction of intestinal flora

Humatin Capsules are indicated in the treatment of the following conditions in adults and adolescents :
- Therapy of non-invasive amoebic infestation of the intestinal lumen

(For infants and children, Humatin Pulvis, powder for oral solution, is available as a suitable pharmaceutical form of paromomycin.)
The official guidelines for appropriate use of antibiotics must be considered.
4.2 Posology and method of administration
Dosage
General dosing recommendations for adults, in each case related to paromomycin :
Prophylaxis of portosystemic encephalopathy
Depending on the severity of the symptoms, adults receive a daily dose of 1,000 to 2,000 mg.
Therapy of portosystemic encephalopathy (e.g. hepatic precoma and hepatic coma)
Depending on the severity of the symptoms, adults receive a daily paromomycin dose of 35 (to 75) mg/kg body weight. In exceptional cases, the daily dose may be increased to a maximum dose of 3,000 mg in patients with normal kidney function.
Duration of therapy : 2 to 6 days or until the symptoms have abated.
In patients with impaired awareness, the required dose may be administered via gastric tube. Humatin Pulvis is best-suited for this purpose.
Preoperative reduction of intestinal flora
During the last 2 days prior to surgery, 4,000 mg paromomycin (16 Humatin Capsules) daily.
In orthograde intestinal lavage, 8,000 to 10,000 mg paromomycin may be administered approximately 1 hour after the end of the lavage and about 12 hours before the planned surgical procedure.
Therapy of non-invasive amoebic infestation of the intestinal lumen
Adults receive a daily dose of 15 to 25 (to 100) mg/kg body weight for at least 5 days or correspondingly higher daily doses for a shorter treatment period.
Dosage example for Humatin Capsules
A patient with 50 kg body weight and a daily dose of 35 mg/kg BW receives a total daily dose of 1,750 mg paromomycin, corresponding to 7 Humatin hard capsules.
The daily dose is divided into several single doses – unless otherwise recommended for special indications – and administered at 6 to 8-hour intervals.
Special patient groups
Patients with hepatic insuffiency
It is usually not necessary to adjust the dosage in the presence of hepatic insufficiency.
Patients with renal insufficiency
Absorbed paromomycin is eliminated primarily via glomerular filtration. Paromomycin should therefore be used with caution in patients with impaired renal function (see **section 5.2**).
Children and adolescents
As no data are available, paromomycin must not be used in children and adolescents below the age of 18 years for the indications "therapy and prophylaxis of portosystemic encephalopathy" and "preoperative reduction of intestinal flora".
Therapy of non-invasive amoebic infestation of the intestinal lumen
Adolescents up to 18 years of age receive a daily dose of 25 to 35 mg/kg body weight for at least 5 days (divided into 3 single doses).
Mode of administration
Humatin hard capsules are best taken after meals.
4.3 Contraindications
Paromomycin must not be used
- in the event of known hypersensitivity to paromomycin or any of the excipients listed under section 6.1. Attention must be paid to a possible cross-hypersensitivity to other aminoglycosides.
- in premature infants and neonates below the age of 1 month due to their immature renal function (see **section 5.2**)
- in children and adolescents below the age of 18 years for the indications "therapy and prophylaxis of portosystemic encephalopathy" and "preoperative reduction of intestinal flora", since no data are available
- in the presence of previous damage to the vestibular or cochlear organs
- in the presence of myasthenia gravis, constipation and ileus
- during pregnancy and lactation

Due to the potential danger of oto- and nephrotoxic side effects, paromomycin may not be administered parenterally (see **also section 4.9**).

4.4 Special warnings and precautions for use
Immediate discontinuation of treatment with paromomycin is required
- when severe, acute hypersensitivity reactions (e.g. anaphylaxis) or rare hypersensitivity reactions (e.g. urticaria) occur
- when severe and persistent diarrhoea occurs during or after treatment (which may be indicative of possible antibiotic-associated pseudomembranous colitis that must be treated immediately)

Paromomycin should be used with particular caution in
- patients with impaired renal function
- long-term treatment with paromomycin (e.g. as a prophylactic in hepatic encephalopathy)
- patients with ulcerations in the gastrointestinal tract
- extensive, inflammatory bleeding lesions of the intestinal mucosa (due to low systemic absorption of paromomycin)

It is recommended to regularly check the hearing function in the above-mentioned patient groups, and to reduce the maintenance dose as appropriate, while the initial dose remains unchanged.
Long-term or repeated administration may lead to superinfections with resistant pathogens and blastomyces.
4.5 Interaction with other medicinal products and other forms of interaction
Due to its minimal gastrointestinal absorption following oral administration, paromomycin has a low potential for systemic interactions with other medicinal products. Theoretically, the same interactions may occur as with systemically administered aminoglycosides.
Neuromuscular blockade may be enhanced and prolonged, when non-depolarizing muscle relaxants are co-administered.
Due to the increased risk of adverse reactions, patients who receive concomitant or subsequent treatment with potentially ototoxic or nephrotoxic agents, such as amphotericin B, colistin, ciclosporin, cisplatin, vancomycin, loop diuretics like ethacrynic acid and furosemide, should be particularly monitored.
4.6 Fertility, pregnancy and lactation
The use of paromomycin is contraindicated during pregnancy. Since a systemic effect cannot be completely ruled out, an embryotoxic/teratogenic risk cannot be ruled out in the first trimester and a fetotoxic risk in the 2nd and 3rd trimesters. Toxic damage to hearing is possible during the entire pregnancy.
Since it is unclear whether the substance is excreted in breast milk, nursing mothers treated with paromomycin should refrain from breast-feeding.
4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
4.8 Undesirable effects
a) Summary of safety profile
The side effects reported most frequently are bowel evacuation (mushy stools) and diarrhoea. In addition, hypersensitivity reactions and antibiotic-associated pseudomembranous colitis have been reported as serious side effects.
b) Summary of side effects in tabular form
The side effects are categorized according to organ class and according to their frequency (number of patients expected to develop a reaction) 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)
Gastrointestinal disorders
Common : Mushy stools, diarrhoea
Rare : Malabsorption syndrome
Not known : Anorexia, nausea, vomiting, stomach cramps, stomach or abdominal pain, pancreatitis
Immune system disorders
Rare : Hypersensitivity reactions, such as urticaria
Not known : Severe, acute hypersensitivity reactions, such as anaphylaxis
Nervous system disorders
Not known : Headache, dizziness
Blood and lymphatic system disorders
Not known : Eosinophilia
Renal and urinary disorders
Not known : Unsettled haematocyturia
Side effects of antibiotics (class effects)
If severe, persistent diarrhoea occurs during or after treatment with paromomycin, this may conceal an antibiotic-associated pseudomembranous colitis requiring immediate treatment. After pseudomembranous enterocolitis has been diagnosed, the attending physician should consider discontinuing therapy with Humatin Capsules and initiating appropriate treatment (use of special antibiotics/chemotherapeutics whose efficacy has been clinically proven). Peristalsis-inhibiting medicinal products are contraindicated.
c) Description of certain side effects
In the event of rare hypersensitivity reactions, such as urticaria, and severe acute hypersensitivity reactions, such as anaphylaxis, treatment with paromomycin must be discontinued immediately, and appropriate emergency measures must be initiated (e.g. administration of antihistamines, corticosteroids, sympathomimetics, and artificial respiration, if needed).
d) Children and adolescents
Based on the available data, the same side effect profile as in adults must be expected in children and adolescents.
4.9 Overdose
Symptoms of overdosage
Since paromomycin is hardly absorbed into the circulating blood if the gastrointestinal mucosa is undamaged, signs of intoxication are hardly to be expected after slight overdosage of Humatin Capsules (see **section 4.3** concerning the possibility of ototoxicity).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Paromomycin is a bactericidal aminoglycoside antibiotic with broad-spectrum actitivity for enteral administration

ATC Code

A07AA06

Mode of action

Like other aminoglycosides, paromomycin has a bactericidal effect. It inhibits protein synthesis of sensitive pathogens by binding to the 30S subunit of the bacterial ribosomes, creating a defective reading of the genetic code and thus inhibiting translocation.

Pharmacokinetic/pharmacodynamic relationship

Efficacy will essentially depend on the time for which substance levels are in excess of the minimal inhibitory concentration (MIC) of the causative pathogen.

Mechanisms of resistance

Most frequent type of resistance

Plasmid-mediated resistance enables resistant bacteria to metabolize paromomycin by means of acetyltransferase, phosphotransferase and adenyltransferase. The resulting metabolites of paromomycin are able to compete with the unchanged paromomycin for intracellular transport, but they do not block the ribosomal protein synthesis of the bacteria.

Second most frequent type of resistance

Reduced permeability of the cytoplasmatic (inner) cell membrane of bacteria may lead to resistance, since in this case paromomycin can no longer reach its site of action.

Rare type of resistance

Changes of the ribosomal binding site of paramomycin may prevent paromomycin binding in rare cases and thus render it ineffective.

There is a complete cross-resistance of pathogens between paromomycin and kanamycin, or between paromomycin and neomycin and a partial cross-resistance between paromomycin and streptomycin.

Breakpoints

The following minimal inhibitory concentrations (MIC) are suggested for paromomycin sulfate :

Pathogen	**MIC**
Sensitive pathogens	≤ 2 mg/l
Pathogens with intermediate sensitivity	No data available
Resistant pathogens	No data available

5.2 Pharmacokinetic properties

Paromomycin is hardly absorbed from the gastrointestinal tract if the mucosa is undamaged. Only very low blood levels have been measured even at high oral doses or with impaired gastrointestinal function or intestinal ulcerations.

After administration of 10 g paromomycin, the maximum concentrations calculated from the serum concentration curves were on average 3.6 µg/ml ± 3.0 µg/ml; the elimination half-life was 2.6 hours; the time curve of the serum concentration could be described by an open one-compartment model. There is no metabolization in the organism. Elimination is primarily in unchanged form via the gastrointestinal tract. Absorbed paromomycin is eliminated via the kidneys primarily in unchanged form. In patients with renal insufficiency as well as in premature infants and neonates, a prolonged half-life must of absorbed paromomycin be expected.

5.3 Preclinical safety data

Chronic toxicity studies have not produced any findings suggesting the emergence of hitherto unknown adverse effects in humans. Like other aminoglycosides, paromomycin may have ototoxic and nephrotoxic effects and may lead to an elevation of hepatic enzymes and to toxic and allergic changes in blood counts.

An *in vitro* study on mammal cells has revealed no evidence of mutagenic potential. No studies are available on reproduction toxicology, carcinogenicity, safety pharmacology and ototoxicology.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin, magnesium stearate, colloidal anhydrous silica, titanium dioxide (E 171), iron oxides and iron hydroxides (E 172), printing ink

6.2 Incompatibilities

None known to date

6.3 Shelf life

5 years

6.4 Special precautions for storage

No special storage conditions are required for these medicinal products.

6.5 Nature and contents of container (s)

Bottle of 28 hard capsules

6.6 Special precautions for disposal (and other handling)

No special requirements