RABEMAX
Instructions
on medical use of the drug

Tradename: Rabemax.
International nonproprietary name: Rabeprazole.
ATX: A02BC04.
Pharmaco-therapeutic group: A drug that reduces the secretion of gastric glands - a proton pump inhibitor.
Compound: *Each enteric-soluble, film-coated tablet contains:*
rabeprazole sodium – 20 mg.
Dosage form: Enteric-soluble, film-coated tablets.
Pharmachologic effect:
Pharmacodynamics:
Rabeprazole belongs to the class of antisecretory substances, benzimidazole derivatives. Suppresses the secretion of gastric juice by specifically inhibiting H+/K + - ATPase on the secretory surface of gastric parietal cells. Blocks the final stage of hydrochloric acid secretion, reducing basal and stimulated secretion, regardless of the nature of the stimulus.
Antisecretory effect after oral administration of 20 mg of rabeprazole occurs within 1 hour and reaches a maximum after 2–4 hours; the inhibition of basal and food-stimulated acid secretion 23 hours after taking the first dose is 62 and 82%, respectively, and lasts up to 48 hours. When you stop taking it, secretory activity is restored within 1–2 days.
During the first 2–8 weeks of rabeprazole therapy, plasma gastrin concentrations increase (reflecting an inhibitory effect on hydrochloric acid secretion) and return to baseline levels 1–2 weeks after discontinuation.
Rabeprazole does not have anticholinergic properties and does not affect the central nervous system, cardiovascular system or respiratory system.
While taking rabeprazole, persistent changes in the morphological structure of enterochromaffin-like cells, the severity of gastritis, the incidence of atrophic gastritis, intestinal metaplasia or the spread of *Helicobacter infection pylori* were not detected.
Pharmacokinetics:
Absorption: Rabeprazole is rapidly absorbed from the intestine, and its Cmax in plasma is reached approximately 3.5 hours after taking a dose of 20 mg . Change $_{in}$ plasma Cmax and AUC values rabeprazole are linear in the dose range from 10 to 40 mg. Absolute bioavailability after oral administration of 20 mg (compared to intravenous administration) is about 52%. In addition, bioavailability does not change with repeated dosing of rabeprazole. In healthy volunteers, $T1_{/2}$ from plasma is about 1 hour (ranging from 0.7 to 1.5 hours), and the total clearance is 3.8 ml/min/kg. In patients with chronic liver damage, AUC doubled compared to healthy volunteers, indicating a decrease in first-pass metabolism, and $T1_{/2}$ from plasma is increased by 2-3 times. Neither the time of taking the drug during the day nor antacids affect the absorption of rabeprazole. Taking the drug with fatty foods slows down the absorption of rabeprazole by 4 hours or more, but neither C_{max} nor the degree of absorption changes.
Distribution: In humans, the degree of binding of rabeprazole to plasma proteins is about 97%.
Metabolism and excretion: In healthy people, no unchanged drug was found in the urine after taking a single oral dose of 20 mg of ^{14}C-labeled rabeprazole. About 90% of rabeprazole is excreted in the urine, mainly in the form of two metabolites: the conjugate mercapturic acid (M5) and carboxylic acid (M 6), as well as in the form of two unknown metabolites identified during toxicological analysis. The remainder of the accepted rabeprazole is excreted in the feces. The total elimination is 99.8%. These data indicate a small excretion of rabeprazole metabolites in bile. The main metabolite is thioether (M1) . The only active metabolite is desmethyl (M3), however this was observed at low concentrations in only one study participant after taking 80 mg rabeprazole .
End-stage renal disease: In patients with stable end-stage renal disease who require maintenance hemodialysis (Cl creatinine <5 ml/min/1.73 m ^{2}), the excretion of rabeprazole is similar to that in healthy volunteers. AUC and Cmax in these patients were approximately 35% lower than in healthy volunteers . On average $T_{1/2}$ rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients undergoing hemodialysis, and 3.6 hours after hemodialysis. Clearance of the drug in patients with kidney disease requiring hemodialysis was approximately twice as high as in healthy volunteers.
Chronic compensated liver cirrhosis: Patients with chronic compensated liver cirrhosis tolerate rabeprazole 20 mg once daily, although AUC_{is} doubled and Cmax is increased by 50% compared with those in sex-matched healthy volunteers.
Elderly patients: In elderly patients, the elimination of rabeprazole is somewhat slower. After 7 days of rabeprazole 20 mg/day in elderly patients , the AUC was approximately twice as high and C_{max} was increased by 60% compared to young healthy volunteers. However, there were no signs of accumulation of rabeprazole .
CYP2C19 polymorphism: In patients with slow metabolism of CYP2C19 , after 7 days of taking rabeprazole at a dose of 20 mg/day, AUC increases by 1.9 times, and $T_{1/2}$ by 1.6 times compared with the same parameters in rapid metabolizers , in while Cmax increases by 40% .
Indications for use:
- gastric ulcer in the acute stage and anastomotic ulcer;
- duodenal ulcer in the acute stage;
- erosive and ulcerative gastroesophageal reflux disease in adults and children over 12 years of age or reflux esophagitis;
- maintenance therapy for gastroesophageal reflux disease;
- non-erosive gastroesophageal reflux disease;
- Zollinger-Ellison syndrome and other conditions characterized by pathological hypersecretion;
- in combination with appropriate antibacterial therapy for eradication *Helicobacter pylori* in patients with peptic ulcer disease.

Contraindications:
- hypersensitivity to rabeprazole, substituted benzimidazoles or auxiliary components of the drug;
- sucrase/ isomaltase deficiency, fructose intolerance, glucose-galactose deficiency;
- pregnancy;
- period of breastfeeding;
- children under 18 years of age, with the exception of GERD (children under 12 years of age).

With caution: severe renal failure; severe liver failure.

Use during pregnancy and breastfeeding:

data on the safety of rabeprazole during pregnancy.

Reproduction studies in rats and rabbits showed no evidence of impaired fertility or fetal developmental defects due to rabeprazole ; however, in rats the drug crosses the placental barrier in small quantities. **Rabemax** is contraindicated during pregnancy.

It is not known whether rabeprazole is excreted in breast milk.

Appropriate studies on the use of the drug during breastfeeding have not been conducted. However, rabeprazole was found in the milk of lactating rats and therefore should not be used by women during breastfeeding.

Side effects:

During clinical studies, the following adverse reactions were observed when taking rabeprazole: headache, dizziness, asthenia, abdominal pain, diarrhea, flatulence, dry mouth, rash.

Adverse reactions are systematized according to the WHO classification: very common (≥1/10); often (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000); frequency unknown (cannot be determined from available data).

From the immune system: rarely - acute systemic allergic reactions (including facial swelling, hypotension, shortness of breath).

From the blood and lymphatic system: rarely - thrombocytopenia, neutropenia , leukopenia.

From the side of metabolism and nutrition: rarely - anorexia; frequency unknown - hyponatremia, hypomagnesemia.

From the nervous system: often - insomnia, headache, dizziness; infrequently – drowsiness, nervousness; rarely - depression; frequency unknown - confusion.

From the side of the organ of vision: rarely - visual impairment.

Vascular disorders: frequency unknown - peripheral edema.

From the respiratory system: often - cough, pharyngitis, rhinitis; infrequently - sinusitis, bronchitis.

From the digestive system: often - abdominal pain, diarrhea, flatulence, nausea, vomiting, constipation; uncommon - dyspepsia, belching, dry mouth; rarely - stomatitis, gastritis, taste disturbance.

From the hepatobiliary system: rarely - hepatitis, jaundice, hepatic encephalopathy.

From the kidneys and urinary tract: infrequently - urinary tract infection; rarely - interstitial nephritis.

From the skin and subcutaneous tissues: rarely - bullous rashes, urticaria; very rarely - erythema multiforme , toxic epidermal necrolysis , Stevens -Johnson syndrome.

Interaction:

of some drugs metabolized in the liver by microsomal oxidation (diazepam , phenytoin, indirect anticoagulants).

Concomitant use of rabeprazole with ketoconazole or itraconazole may lead to a significant decrease in plasma concentrations of antifungal drugs.

Concomitant use of proton pump inhibitors (PPIs) with atanasavir is not recommended, because the effects of atanasavir are significantly reduced.

Rabeprazole inhibits the metabolism of cyclosporine.

When taking a PPI and methotrexate simultaneously, an increase in the concentration of the latter and/or its metabolite hydroxymethotrexate and an increase in $T1_{/2}$ can be expected .

When rabeprazole , amoxicillin and clarithromycin were co-administered, $_{the}$ AUC and Cmax values for clarithromycin and amoxicillin were similar when comparing combination therapy with monotherapy . AUC and Cmax indicators _ rabeprazole increased by 11 and 34%, respectively, and the AUC and C_{max} of 14-hydroxyclarithromycin (the active metabolite of clarithromycin) increased by 42 and 46%, respectively. This increase in indicators was not considered clinically significant.

The simultaneous use of rabeprazole and antacid suspensions containing aluminum and/or magnesium hydroxide does not lead to a clinically significant interaction.

Directions for use and doses

Inside. Rabemax tablets should be swallowed whole**.** It has been established that neither time of day nor food intake affects the activity of rabeprazole.

For gastric ulcers in the acute stage and anastomotic ulcers, it is recommended to take 10 or 20 mg orally once a day. Usually cure occurs after 6 weeks of therapy, but in some cases the duration of treatment can be increased by another 6 weeks.

For duodenal ulcers in the acute stage, it is recommended to take 20 mg orally once a day. In some cases, the therapeutic effect occurs when taking 10 mg 1 time per day. The duration of treatment is from 2 to 4 weeks. If necessary, the duration of treatment can be increased by another 4 weeks .

When treating erosive GERD or reflux esophagitis, it is recommended to take 10 or 20 mg orally once a day. The duration of treatment is from 4 to 8 weeks . If necessary, the duration of treatment can be increased by another 8 weeks .

For maintenance therapy of GERD, it is recommended to take 10 or 20 mg orally once a day. The duration of treatment depends on the patient's condition.

For non-erosive gastroesophageal for reflux disease without esophagitis, it is recommended to take 10 or 20 mg orally once a day.

If symptoms do not disappear after 4 weeks of treatment, the patient should be further examined. After relief of symptoms, to prevent their subsequent occurrence, the drug should be taken orally at a dose of 10 mg 1 time per day as required.

Zollinger-Ellison syndrome and other conditions characterized by pathological hypersecretion, the dose is selected individually. The initial dose is 60 mg per day, then the dose is increased and the drug is prescribed at a dose of up to 100 mg per day in a single dose or 60 mg 2 times a day. For some patients, fractional dosing of the drug is preferable. Treatment should be continued as clinically necessary. In some patients with Zollinger-Ellison syndrome , the duration of treatment with rabeprazole was up to one year.
For eradication Helicobacter pylori is recommended to be taken orally 20 mg 2 times a day according to a specific regimen with appropriate combinations of antibiotics. The duration of treatment is 7 days.
Patients with renal and hepatic insufficiency: No dose adjustment is required in patients with renal insufficiency.

In patients with mild to moderate hepatic impairment, blood concentrations of rabeprazole are usually higher than in healthy volunteers. When prescribing **Rabemax** to patients with severe liver failure, caution should be exercised.
Elderly patients: No dose adjustment is required.
Children: The safety and effectiveness of rabeprazole 20 mg for the short-term (up to 8 weeks) treatment of GERD in children 12 years of age and older is confirmed by extrapolation of the results of adequate and well-controlled studies confirming the effectiveness of rabeprazole in adults and safety and pharmacokinetic studies in pediatric patients.
The recommended dose for children aged 12 years and over is 20 mg once daily for up to 8 weeks .
The safety and effectiveness of rabeprazole for the treatment of GERD in children younger than 12 years of age have not been established. The safety and effectiveness of rabeprazole for other indications has not been established in pediatric patients.

Overdose

Symptoms: There is minimal evidence of intentional or accidental overdose.
Treatment: Rabeprazole binds well to plasma proteins and is therefore poorly excreted during dialysis. In case of overdose, symptomatic and supportive treatment should be provided. A specific antidote for rabeprazole is unknown.

special instructions:

rabeprazole therapy does not exclude the presence of malignant neoplasms in the stomach.
Rabemax tablets should be swallowed whole **.** It has been established that neither time of day nor food intake affects the activity of rabeprazole .
In a special study in patients with mild or moderate liver dysfunction, there was no significant difference in the incidence of side effects of the drug **Rabemax** from that of healthy individuals matched by sex and age, but despite this, caution is recommended when first prescribing **Rabemax** to patients with severe impairment liver functions.
Patients with impaired renal or liver function do not require dose adjustment of **Rabemax**. AUC rabeprazole in patients with severe liver dysfunction is approximately twice as high as in healthy patients.
Hypomagnesemia: Symptomatic or asymptomatic cases have been reported in rare cases when treated with PPIs for at least 3 months. hypomagnesemia. In most cases, these reports were received one year after therapy. Serious adverse events included tetany, arrhythmia, and seizures. Most patients required treatment for hypomagnesemia, including magnesium replacement and discontinuation of PPI therapy. In patients who will be receiving long-term treatment or who are taking PPIs with drugs such as digoxin or that can cause hypomagnesemia (for example, diuretics), monitoring of magnesium levels is necessary before starting PPI treatment and during treatment.
Fractures: PPI therapy may increase the risk of osteoporosis-related fractures of the hip, wrist, or spine. The risk of fractures was increased in patients receiving high doses of PPIs for a long time (a year or more).
Concomitant use of rabeprazole with methotrexate : According to the literature, simultaneous use of PPIs with methotrexate (primarily in high doses) can lead to an increase in the concentration of methotrexate and/or its metabolite hydroxymethotrexate and increase $T1_{/2}$, which can lead to methotrexate toxicity. If high doses of methotrexate are required, temporary discontinuation of PPI therapy may be considered.
Infections caused by Salmonella , Campylobacter and Clostridium difficile: PPI therapy may lead to an increased risk of gastrointestinal infections, such as those caused by *Salmonella , Campylobacter* , and *Clostridium difficile.*
Effect on the ability to drive vehicles and operate machinery: Based on the characteristics of pharmacodynamics Rabeprazole and its profile of undesirable effects, it is unlikely that **Rabemax** affects the ability to drive vehicles and operate machinery. However, if drowsiness occurs, these activities should be avoided.

Release form:

tablets , 20 mg. 10 are placed in a blister pack.

Storage conditions:

In a place protected from light, at a temperature not exceeding 25 °C.
Keep out of the reach of children.

Best before date:

3 years.
Do not use after the expiration date stated on the package.

Conditions for dispensing from pharmacies:

On prescription.

Made for:
MAXX-PHARM LTD.
London, Great Britain