Translation from Russian into English
The text of translation

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

INSTRUCTION

on usage of the drug preparation for medical use

PANGROL ® 25000

Registration number:

Trade name of preparation: Pangrol® 25000

International non-proprietary name

or grouping name: Pancreatine

Dosage form: enterosoluble capsules

Composition per 1 capsule:

(mini-tablets coated with enterosoluble coating):

Core:
Active substance:
Pancreatine – 356,10 mg
with a minimal activity of:

lipase	25000 U
amylase	22500 U
protease	1250 U

List of excipients: Sodium croscarmellose - 11,87 mg, Microcrystalline cellulose - 19,77 mg, Hydrogenated castor oil - 3,96 mg, Anhydrous colloidal silica dioxide – 1,97 mg, Magnesium stearate – 1,97 mg.
Coating: Copolymer of metacrylic acid and ethylacrylate (1 : 1), 30 % dispersion – 57,9 mg, Triethylcitrate – 5,82 mg, Simethicone emulsion 30 % (dry mass) – 0,036 mg, Talc – 11,63 mg;

Capsule:
Shell: Gelatin – 65,40 mg, Titanium dioxide (E 171) – 0,30 mg, Colorant yellow ferric oxide (E 172) – 0,30 mg, Colorant red ferric oxide (E 172) - 0,02 mg;
Cap: Gelatin – 42,900 mg, Titanium dioxide (E 171) – 0,800 mg, Colorant quinolinic yellow (E 104) – 0,300 mg, Indigo carmine (E 132) – 0,003 mg.

Description:

Non-transparent hard gelatin capsules of cylindrical shape with semispherical ends, № 0: capsule shell is light-orange, capsule cap is yellowish-green.
Capsules contents: mini-tables of cylindrical shape, coated with enteric-soluble light-beige coating having a bright surface.

Pharmacotherapeutic group: Digestive enzymatic agent.

ATC code: A09AA02.

Pharmacological properties:
Pharmacodynamics:
The active substance of Pangrol® 25000 preparation is pancreatine, which is powdered porcine pancreas. The pancreatic enzymes that are components of the active substance promote the splitting of fats, carbohydrates, and proteins coming with meals. Pancreatine performing the proteolytic, aminolytic, and lipolytic activity compensates for the enzymatic insufficiency of the pancreatic gland, improves the functional condition of gastrointestinal tract (GIT) and normalizes digestive processes.
Pharmacokinetics:

Gelatin Pangrol® 25000 capsules rapidly dissolve in the stomach to release enteric-coated mini-tablets (coated with acid – resistant coating). Thus, enzymes are protected of their inactivation in the acid gastric medium. The principle of action of a multiunit dose is the mixing of mini-tablets with the intestinal content and finally the better distribution of the enzymes. The disintegration of enteric shell of mini-tablets and activation of enzymes occur at the neutral or slightly alkaline pH value inside the small bowel. Pancreatine is not absorbed in the GIT and is excreted with faeces.

Indications for Usage

Replacement therapy for pancreas exocrine insufficiency in adult and pediatric patients in the following conditions:

- chronic pancreatitis;
- mucoviscidosis;
- pancreas cancer;
- conditions following operative interventions in the pancreatic gland and stomach (partial or total resection of the organ);
- after irradiation of the GIT organs associated with the impairment of digestive processes, flatulence, diarrhea (as a part of combined therapy);
- neoplasm-induced ductal obstruction, such as obstruction of pancreas ducts or the common bile duct;
- Shwachman-Diamond syndrome;
- subacute pancreatitis;
- other diseases associated with the pancreas exocrine insufficiency.

Relative enzymatic insufficiency in the following cases and conditions:

- functional abnormalities of the GIT, in acute intestinal infections, and in the irritated intestine syndrome;
- ingestion of difficult-to-digestible vegetable or fat-containing meals;

Preparation for roentgenological and ultrasonic investigations of organs of the abdominal cavity.

Contraindications

- acute pancreatitis,
- exacerbation of chronic pancreatitis;
- Individual hypersensitivity to the pancreatine of the porcine origin or to other ingredients of preparation.

Use during pregnancy and lactation
Pregnancy:

There is a lack of clinical data on the treatment of pregnant females with preparations, which contain pancreatic enzymes. Within preclinical studies, the absorption of pancreatic enzymes of the porcine origin was not revealed, thus, the toxic influence of the agent on the reproductive function and fetus development is not estimated. Pangrol® 25000 should be prescribed to pregnant females only if expected maternal benefits overweigh possible fetal or infant risks

Lactation:

Judging from the results of preclinical studies, none adverse effects of pancreatic enzymes of the porcine origin were revealed, thus, no negative effects of preparation via the breast milk on the infant are expected. Within the breast-feeding period, the administration of pancreatic enzymes is permissible.

Administration mode and dosages

The doses of the **Pangrol® 25000** preparation should be individually chosen depending on the severity of disease and on the volume and composition of a diet.

Unless otherwise prescribed, ***adults*** should take 1 – 2 capsules of the **Pangrol® 25000** preparation during each meal, swallowed capsules as a whole, without breaking and chewing them and having sufficient amount of water (a glass of water, for example).

On difficult swallowing (for example, in babies and infants or elderly patients), the capsule should be opened by detaching the shell off the cap, and its contents should be removed, in a glass, for example, and the contents (mini-tablets) should be added to some amount of a liquid food that does not require chewed (for example, apple sauce or fruit juice) or be taken with liquid. Any mixture of mini-tablets with food or liquid is not to be stored (it should be taken just after its preparation).

The increase of the dosage of preparation should be made under physician's supervision only, taking into consideration the symptoms' dynamics (for example, minimization of steatorrhea and maintenance of a good nutritional status).

A daily enzyme dose of 15000-20000 units of lipase per kg of body weight should not be exceeded.

The treatment duration is determined by the physician and depends on the course of the disease.

Children: the mode of dosage and the treatment duration are determined by the physician depending on the degree of the digestive insufficiency and the dietary composition calculated as of 500 – 1000 lipase units per kg of a child bodyweight per each meal.

Administration in mucoviscidosis:

The dose of the **Pangrol® 25000** preparation depends on the body weight, and at the beginning of therapy it should be 1000 lipase units/kg per each meal for children aged under 4 years; and 500 lipase units/kg during each meal for children above 4 years.

The dose of preparation should be determined individually depending on the severity of symptoms, the results of steatorrhea monitoring and good nutritional maintenance. In most patients, the dose should not exceed 10000 lipase units/kg of body weight daily, or 4000 lipase units/g of consumed fat.

Side effects and adverse reactions

The frequency of possible side effects is classified under the headings, depending on the occurrence of side effects in descending order: frequently ($\geq$ 1/100, < 1/10), infrequently ($\geq$ 1/1000, < 1/100), rarely ($\geq$ 1/10000, < 1/1000), very rarely (< 1/10000), including spontaneous reports.

Gastrointestinal tract:

Frequently: nausea, vomiting and abdominal swelling.

Gastrointestinal disorders are connected, mainly, with the main disease. The frequency of the following side effects was lower than or similar to that of placebo administration:
Very frequently: abdominal pain; *Frequently:* diarrhea.
Skin and soft tissues:
Rarely: rash;
Itching, urticaria – *insufficient data for evaluation of the frequency of side effects.*

Overdosage
Symptoms: Administration of large doses of pancreatic enzymes may be associated with hyperuricuria and hyperuricemia in patients with mucoviscidosis.
Treatment: discontinuance of the drug, symptomatic therapy.

Drug interactions / Interaction with other medical products
There are no reports on its drug or other interactions.

Special precautions
There are reports on strictures of the ileum and the caecum and colitis occurring in patients with mucoviscidosis who receive high doses of pancreatin preparations (fibrosing colonopathy).
As a preventive measure, all unusual abdominal cavity symptoms or changes of the symptoms of the main disease that may occur in patients should be monitored in order to exclude the lesions of large intestine, particularly, if the patient takes more than 10000 lipase units/kg of bodyweight daily.

Effects on the Capacity of Driving Motor Vehicles and Handle Machinery and Mechanisms
Pangrol® 25000 does not affect the capacity of performing potentially hazardous activities which may require elevated concentration of attention and the rapidness of psychomotor reactions.

Pack presentation
Enterosoluble capsules, 25000 U.
20, 50 or 100 capsules per a polypropylene bottle with a polyethylene cap equipped with an exsiccant.
1 bottle with leaflet insert in a carton box.

Storage conditions
Keep at the light-protected place at temperature below 25 ^{o}C.
Keep the drug preparation out of the reach of children!

Shelf-life
2 years.
Do not use after the expiry date indicated on a pack.

Sale conditions:
A physician's prescription is not required.
Manufacturing company:

Adare Pharmaceuticals S.r.l.,Italy
Via Martin Luther King, 13
20060, Pessano con Bornago
Milan, Italy

Is manufactured according to the technological method of «Eurand Minitabs® Technology»

Batch release control
Berlin - Chemie AG
Glienicker Weg 125
12489, Berlin, Germany

Address for raising claims:
123317, Moscow, Presnenskaya quay, 10, BC “Tower on Quay”, Block B.
Phone: (495) 785-01-00, Fax: (495) 785-01-01.

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I hereby confirm that the invoiced translation:
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is correct and complete from a content and linguistic point of view. The quality of the translation is guaranteed.
Yours faithfully,
(*signature*) Ludmila Kshevinskaya