

PROSOGAN® INJECTION

Lansoprazole 30 mg

PROSOGAN® injection are white to yellowish-white mass or powder. Each vial contains lansoprazole 30 mg.

MECHANISM OF ACTION

Lansoprazole is firstly transferred to the acid-producing region of the gastric mucosal parietal cells, and transformed into an activated form through conversion reaction by acid. This reaction product is considered to combine with the SH-groups of (H⁺, K⁺)-ATPase which is locally located in the acid-producing region and playing a role of the proton pump, suppressing the enzyme activity to inhibit the acid secretion.

It has been reported that blood coagulation and platelet aggregation capacities are severely impaired under acidic conditions, and that fibrin formed as a result of blood coagulation is dissolved by pepsin under acidic conditions. Lansoprazole is considered to increase gastric pH, thereby improving blood coagulation and platelet aggregation capacities and inhibiting peptic activity, resulting in suppression of bleeding.

Also, lansoprazole is considered to increase gastric pH by inhibiting acid secretion, thereby promoting repair of injured mucosa, which is inhibited under acidic conditions.

Inhibiting activity on gastric bleeding

In rats (intravenous dose), lansoprazole shows an inhibiting activity on gastric bleeding due to hemorrhagic shock.

Inhibiting activity on formation of gastric mucosal injury

In rats (intravenous dose), lansoprazole inhibits gastric mucosal injury due to aspirin or indometacin.

Inhibiting activity on gastric acid secretion (24-hour gastric pH monitoring)

By intravenous administration of lansoprazole at a dose of 30 mg twice a day to healthy adults, continuous inhibition of gastric acid secretion is observed. The rates of 24-hour gastric pH 4 holding time (the time that the gastric pH is 4 or over) are similar between intravenous injection (approximately 3 minutes) and intravenous drip infusion (30 minutes).

In addition, the gastric acid secretion inhibiting effect (pH 4 holding time every 24 hours) after intravenous administration of lansoprazole at a dose of 30 mg twice a day to healthy adults whose metabolizer types for lansoprazole were identified as EM or PM is as follows: The rates of pH 4 holding time are 56-69% in EMs and 90% in PMs on day 1 and 80-89% in EMs and 98% in PMs on day 5.

PHARMACOKINETICS

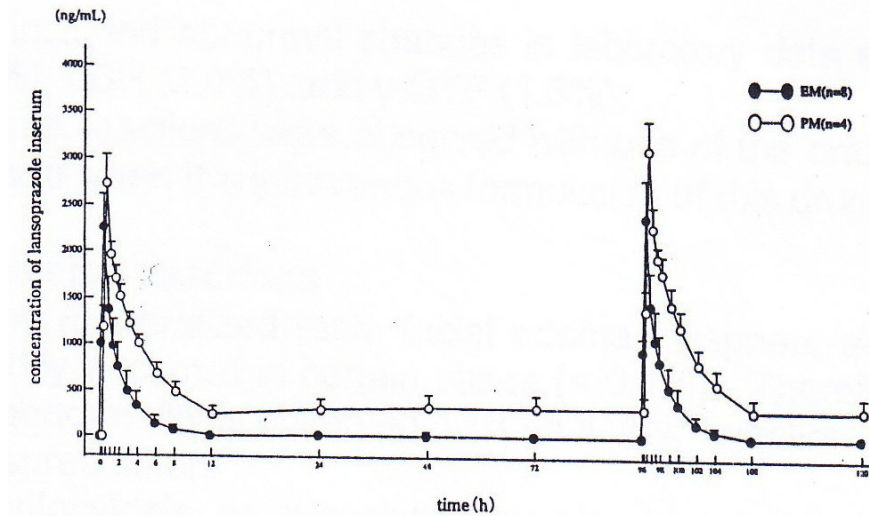
Blood concentrations

The serum concentration of lansoprazole after intravenous administration of PROSOGAN® Injection 30 mg varies among individuals.

The following figure shows the serum concentration of lansoprazole after intravenous drip of 30 mg of lansoprazole twice a day for 5 days to 12 healthy male adults classified into either extensive metabolizer (EM) group (8 subjects) in which lansoprazole is rapidly metabolized or poor metabolizer (PM) group (4 subjects) in which the drug is slowly metabolized according to CYP2C19 genotype.

	Metabolizer Type	AUC ₀₋₁₂ (ng h/mL)	C _{max} (ng/mL)	t _{1/2} (h)
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day 1	EM	4386±1335	2262±354	1.5±0.4
	PM	10415±1159	2727±315	4.0±0.7
day 5	EM	4939±1541	2414±406	1.6±0.5
	PM	12579±1939	3134±316	4.2±1.1



Protein binding rate

The human serum protein binding rate of lansoprazole at the concentration range of 0.05 to 5 µg/mL is approximately 98%.

Metabolism

Lansoprazole is mainly metabolized by CYP2C19 and CYP3A4. It has been reported that there is genetic polymorphism of CYP2C19, and the frequency of poor metabolizers among Asian-Mongolian populations including Japanese is approximately 10-20%.

Urinary excretion

After single intravenous administration of 30 mg of lansoprazole to healthy male adults (9 subjects), no unchanged compound was detected in the urine; all detected were metabolites. The accumulated urinary excretion rate up to 24 hours after administration was 12-17%.

INDICATIONS

Patients with the following diseases who are unable to take the oral formulations :
Gastric ulcer, duodenal ulcer, acute stress ulcer, and acute gastric mucosal lesion accompanied by bleeding.

DOSAGE AND ADMINISTRATION

Usually, for adults, PROSOGAN[®] Injection 30 mg is mixed with isotonic sodium chloride solution or 5% glucose injection and administered by intravenous drip twice a day; alternatively, PROSOGAN[®] Injection 30 mg is dissolved in 20 mL of isotonic sodium chloride solution or 5% glucose injection and administered slowly by intravenous injection twice a day.

1. As PROSOGAN[®] Injection 30 mg was shown to have high hemostatic effect based on the data up to 3 days after starting treatment, once the patient is able to take medications orally, therapy should be switched to an oral formulation and this drug should not be administered aimlessly for a long period.
2. There is no clinical experience of treatment over 7 days in Japanese clinical trials

CONTRAINDICATIONS

PROSOGAN[®] Injection 30 mg is contraindicated in the following patients :

1. Patients with a history of hypersensitivity to any of the ingredients of this drug.
2. Patients who are receiving atazanavir sulfate.

Contraindications for coadministration

PROSOGAN[®] Injection 30 mg should not be coadministered with the following drug :

Drugs	Signs, Symptoms, and Treatment	Mechanisms and Risk Factors
Atazanavir sulfate	Effect of atazanavir sulfate may be diminished.	Gastric antisecretory effect of PROSOGAN [®] Injection 30 mg may reduce solubility of atazanavir sulfate, resulting in a decrease in the blood concentration of atazanavir.

ADVERSE REACTIONS

Adverse reactions, including abnormalities in laboratory data, were observed in 31 (14.0%) of 221 patients given lansoprazole at a dose of 30 mg twice a day in clinical trials before approval. Main adverse reactions included abnormal changes in laboratory data such as increased ALT (GPT) (6.2%), AST (GOT) (5.7%), LDH (2.0%), and γ -GTP (1.5%).

Since the following adverse reactions were observed with use of the oral formulations of lansoprazole, caution should be exercised when the intravenous formulation of this drug is administered.

Clinically significant adverse reactions

1. Anaphylactic reactions (generalized rash, facial edema, dyspnea, etc.) may occur (< 0.1%), and shock has consequently occurred in certain cases (< 0.1%). Therefore, close observation should be made, and if any abnormality is observed, PROSOGAN[®] Injection 30 mg should be discontinued and appropriate measures taken.
2. Pancytopenia, agranulocytosis or hemolytic anemia may occur (<0.1%). Granulocytopenia, thrombocytopenia or anemia may occur (0.1% - <5%). Therefore, close observation should be made, and if any abnormality is observed, such appropriate measures as discontinuation of PROSOGAN[®] Injection 30 mg should be taken.
3. Severe hepatic dysfunction with jaundice, increased AST(GOT), ALT(GPT), etc., may occur (<0.1%). Therefore, close observation should be made. If any abnormality is observed, PROSOGAN[®] Injection 30 mg should be discontinued and appropriate measures taken.
4. Toxic epidermal necrolysis (Lyell syndrome) and oculomucocutaneous syndrome (Stevens-Johnson syndrome) (<0.1%) may occur. Therefore, close observation should be made. If any abnormality is observed, PROSOGAN[®] Injection 30 mg should be discontinued and appropriate measures taken.
5. Interstitial pneumonia (<0.1%) may occur. Therefore, if fever, coughing, dyspnea, abnormal lung sound (crepitation), etc., are observed, such examinations as chest X-ray should immediately be performed, and PROSOGAN[®] Injection 30 mg should be discontinued. Appropriate measures, such as treatment with a corticosteroid preparation, should be taken.
6. Interstitial nephritis (frequency unknown) may occur, resulting in acute renal failure in some cases. Therefore, pay attention to renal function test values (increases in BUN, creatinine, etc), and if any abnormality is observed, PROSOGAN[®] Injection 30 mg should be discontinued and appropriate measures taken.

Other adverse reactions

If any of the following adverse reactions is observed, appropriate measures such as discontinuation of PROSOGAN® Injection 30 mg should be taken.

	0.1% - <5%	<0.1%	Frequency unknown
1) Hypersensitivity	Rash or pruritus		
2) Hepatic	Increased AST(GOT), ALT(GPT), AL-P, LDH or g-GTP		
3) Hematologic	Eosinophilia		
4) Gastrointestinal	Constipation, diarrhea, thirst or feeling of enlarged abdomen	Nausea, vomiting, anorexia, abdominal pain, candidiasis, or taste abnormality	Stomatitis, glossitis, or colitis ^{Note)}
5) Psychoneurologic	Headache or sleepiness	Depressed state, insomnia, dizziness or tremor	
6) Others	Fever, increased total cholesterol or uric acid	Gynecomastia, edema, malaise, numbness of tongue or lips, numbness of limbs, muscle pain or alopecia	Blurred vision, weakness or arthralgia

Note) If diarrhea persists, there is a possibility that the patient developed colitis with histological findings of the large intestinal submucosa such as thickening of collagen bands and/or infiltration of inflammatory cells, even though no abnormality in the intestinal mucosa was observed on endoscopy. Therefore, PROSOGAN® Injection 30 mg should be promptly discontinued.

Careful Administration

PROSOGAN® Injection 30 mg should be administered with care in the following patients :

1. Patients with a history of drug hypersensitivity.
2. Patients with hepatic disorders. (A delay in the metabolism and excretion of PROSOGAN® Injection 30 mg may occur).
3. Elderly patients (See Use in the Elderly)

Important Precautions

1. At the treatment, the course of the disease should be closely observed and the minimum therapeutic necessity should be used according to the disease condition. If PROSOGAN® Injection 30 mg is ineffective, it should be switched to another treatment.
2. If the patient has projectile bleeding or oozing bleeding, or is considered at risk for rapid bleeding such as the case of presence of exposed blood vessels, the patient should undergo endoscopic hemostasis such as heater probe or clipping.

Precautions for coadministration

PROSOGAN® Injection 30 mg should be administered with care when coadministered with the following drugs :

Drugs	Signs, Symptoms, and Treatment	Mechanisms and Risk Factors
Theophylline	A decrease in the concentration of theophylline in blood may occur.	PROSOGAN® Injection 30 mg is considered to induce a hepatic drug-metabolizing enzyme, resulting in enhancement of the metabolism of theophylline.
Tacrolimus hydrate	An increase in the concentration of tacrolimus in blood may occur.	PROSOGAN® Injection 30 mg is considered to competitively inhibit tacrolimus metabolism by hepatic drug-metabolizing enzymes.
Digoxin Methyldigoxin	Effects of these drugs may be enhanced.	Gastric antisecretory effect of PROSOGAN® Injection 30 mg may inhibit hydrolysis of digoxin, resulting in an increase in the blood concentration of digoxin.
Itraconazole Gefitinib	Effects of these drugs may be diminished.	Gastric antisecretory effect of PROSOGAN® Injection 30 mg may lead to a decrease in the blood concentration of these drugs.
Phenytoin Diazepam	It has been reported in the administration of a similar drug (omeprazole) that coadministration with either one of these drugs delayed the metabolism and excretion of such drugs.	

DRUG INTERACTIONS

PROSOGAN® Injection 30 mg is metabolized mainly by hepatic drug-metabolizing enzyme CYP2C19 and CYP3A4.

Gastric antisecretory effect of PROSOGAN[®] Injection 30 mg may promote or inhibit absorption of concomitant drugs.

Use in the Elderly

Since physiological function is generally decreased in elderly patients, PROSOGAN[®] Injection 30 mg should be carefully administered.

Use during Pregnancy, Delivery or Lactation

1. PROSOGAN[®] Injection 30 mg should be used in pregnant women or women having possibilities of being pregnant only if the expected therapeutic benefit is thought to outweigh any possible risk. (In animal studies [rats, oral dose], higher plasma concentration of lansoprazole in the fetus than in the mother animal was observed. In pregnant rabbits [oral doses of 30 mg/kg/day], an increased fetus death rate was observed).
2. It is advisable to avoid the administration of PROSOGAN[®] Injection 30 mg to nursing mothers. However, when the administration is indispensable, nursing should be discontinued. (It has been reported in animal studies [rats, oral dose] that lansoprazole is transferred to mother's milk).

Pediatric use

The safety of PROSOGAN[®] Injection 30 mg in children has not been established (no clinical experience).

Precautions concerning Use

1. Route of administration :
PROSOGAN[®] Injection 30 mg should be used only by intravenous route.
2. After dissolution :
PROSOGAN[®] Injection 30 mg should be used immediately after dissolution and the dissolved solution should not be stored since the solution may deteriorate over time.
3. Incompatibility :
PROSOGAN[®] Injection 30 mg should not be mixed with solutions, infusion fluid, replacement fluid, and other medicinal products except isotonic sodium chloride solution or 5% glucose injection since discoloration and precipitation may occur in the mixed solution.
4. Method of administration :
A dedicated infusion line should be used for the administration of PROSOGAN[®] Injection 30 mg. The infusion line should not be shared with other drugs. If it is inevitable to administer PROSOGAN[®] Injection 30 mg using the infusion line for other drugs via a Y-site, the infusion of other drugs should be stopped and the line should be flushed by isotonic sodium chloride solution or 5% glucose injection before and after administration of PROSOGAN[®] Injection 30 mg.

Other Precautions

1. It has been reported from abroad that visual disturbance occurred with use of a similar drug (omeprazole).
2. In an animal study in which 50 mg/kg/day (about 100 times the clinical dose) of lansoprazole was given to rats by gavage administration for 52 weeks, benign testicular

interstitial cell tumors were observed in one animal. In another study in which 15 mg/kg/day or more was given to rats by gavage for 24 months, an increase in the frequency of benign testicular interstitial cell tumors was observed and, in which 5 mg/kg/day or more was given, carcinoid tumors in the stomach were observed. In addition, in the group of female rats given 15 mg/kg/day or more of lansoprazole and the group of male rats given 50 mg/kg/day or more, an increase in the frequency of retinal atrophy was observed. Testicular interstitial cell tumors and retinal atrophy were not observed in carcinogenicity studies in mice, as well as in toxicity studies in dogs or monkeys. Thus, these changes are considered to be specific to rats.

3. The administration of PROSOGAN® Injection 30 mg may mask the symptoms of gastric cancer. It is, therefore, necessary to ascertain the ulcer is not of a malignant nature before initiating the administration of this drug.

STORAGE

Store at a temperature not exceeding 25°C (under controlled air-conditioning)

EXPIRE DATE : 3 YEARS

PACKAGING

Box contains 1 vial.

REGISTRATION NO.

DKI xxxxxxxx

ON MEDICAL PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

**Imported and packed by PT. Takeda Indonesia, Bekasi, Indonesia
Manufactured by Mochida Pharmaceutical Plant Co., Ltd, Tochigi, Japan
For Takeda Pharmaceutical Company Limited, Osaka, Japan**