PROSOGAN® INJECTION
Lansoprazole 30 mg

1 NAME OF THE MEDICINAL PRODUCT

PROSOGAN® INJECTION 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Each vial contains 30 mg of Lansoprazole.

3 PHARMACEUTICAL FORM

White to yellowish-white mass or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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).

4.2 Posology and method of 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.

Special Patient Populations

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). Intravenous dose reduction in patients with severe hepatic disease should be considered. These patients should be kept under regular supervision.
3. Elderly patients : since physiological function is generally decreased in elderly patients, PROSOGAN® Injection 30 mg should be carefully administered. A daily dose of 30 mg should not be exceeded. Renal impairment patients do not require dosage adjustment.
4. Pediatric use : The safety of PROSOGAN® Injection 30 mg in children has not been established (no clinical experience).

4.3 Contraindications

Patients with a history of hypersensitivity to the active ingredients or to any of the excipients.

4.4 Special warnings and special precautions for use

Bone fracture: PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who receive high-dose, defined as multiple daily doses, and long term PPI therapy (a year or longer).

Clostridium difficile: PPI therapy may be associated with an increased risk of Clostridium difficile infection.

Hypomagnesemia: has rarely been reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious adverse events include tetany, arrhythmias and seizures. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia *(see Undesirable Effects, 4.8)*. In most patients, treatment of hypomagnesemia and hypomagnesemia associated hypocalcemia and/or hypokalemia required magnesium replacement and discontinuation of the PPI.

Hepatic Impairment: This drug should be administered with caution to patients with severe hepatic disorder.

HIV Protease inhibitors : co-administration of Prosogan Injection is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate: Concomitant use with high-dose Methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Gastric malignance: Symptomatic response to lansoprazole does not preclude the presence of gastric malignancy.

Influence on Vitamin B12 Absorption: Daily treatment with any acid-suppressing medications over a prolonged period of time (several years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

Interference with laboratory tests: Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and erythema multiforme have been reported in association with the use of PPIs (*see Undesirable Effects, 4.8)*. Discontinue lansoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Subacute Cutaneous Lupus Erythematosus (SCLE) : Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping the product.

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 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.

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.

4.5 Interaction with other medications and other forms of interaction

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

Tacrolimus*:*
Concomitant administration of Prosogan Injection and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Drugs that Inhibit or Induce CYP2C19
Inhibitors of CYP2C19 such as fluvoxamine would likely increase the systemic exposure of PROSOGAN® Injection 30. Inducers of CYP2C19 would likely decrease the systemic exposure to PROSOGAN® Injection 30.

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

Patient monitoring should be taken in coadministration of PROSOGAN® Injection 30 mg with theophylline.

Drugs with pH Dependent Absorption Pharmacokinetics : PROSOGAN® Injection 30 mg may interfere with the absorption of other drugs where gastric pH is an important determinant of oral availability.

HIV Protease inhibitors : co-administration of PROSOGAN® Injection 30 mg is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate : Concomitant use with high-dose Methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Clopidogrel : Concomitant administration of PROSOGAN® Injection 30 mg and clopidogrel in health subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of PROSOGAN® Injection 30 mg.

Warfarin : Co-administration of lansoprazole 60 mg and warfarin did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with Lansoprazole and warfarin concomitantly may need to be monitored for increase in INR and prothrombin time.

4.6 Pregnancy (Category B) and 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. There is insufficient data to recommend the administration of PROSOGAN® Injection 30 mg during pregnancy. (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 unknown whether PROSOGAN® Injection 30 mg is excreted in human breast milk.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).

4.7 Effects on ability to drive and use machines

PROSOGAN® Injection 30 mg is not expected to adversely affect the ability to drive or use machines.

4.8 Undesirable effects

Adverse Drug Reactions

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

Blood and lymphatic system disorders: Pancytopenia*, Agranulocytosis* * or Hemolytic anemia, Granulocytopenia, Leukopenia*,Thrombocytopenia* or Anemia and Eosinophilia.

Immune system disorders: Anaphylactic reaction*
Metabolism and nutrition disorders: Hyponatremia*, Hypomagnesemia, Hypocalcemia*† and Hypokalemia*†

Nervous system disorders: Headache, Depressed state, Insomnia and Dizziness or Tremor.

Gastrointestinal disorders: Constipation, Diarrhea, Thirst or feeling of enlarged abdomen, Flatulence, Nausea, Vomiting, Anorexia, Abdominal pain, candidiasis or Taste abnormality, Stomatitis, Glossitis and Microscopic colitis*

Hepatobiliary disorders: Abnormal liver function test values, Hepatitis, Jaundice and Elevation of AST (GOT), ALT (GPT), Alkaline-P, LDH and γ-GTP values

Skin and subcutaneous tissue disorders: Rash, Pruritus, Steven-Johnson Syndrome*, Toxic Epidermal Necrolysis*, Cutaneous lupus erythematosus*,Drug reaction with eosinophilia and systemic symptoms (DRESS)* ,Acute generalized exanthematous pustulosis (AGEP)* and Erythema multiforme.

Renal and urinary disorders: Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)

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 and Weakness or arthralgia

* Postmarketing events
† Hypocalcemia and/or hypokalemia may be related to the occurrence of hypomagnesemia (see Special Warnings and Special Precautions for Use, 4.4)

4.9 Overdose

PROSOGAN® Injection 30 mg is not removed from the circulation by hemodialysis. Daily doses of up to 90 mg of PROSOGAN® Injection in trials have been administered without significant undesirable effects. If an overdose occurs, treatment should be symptomatic and supportive.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

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.

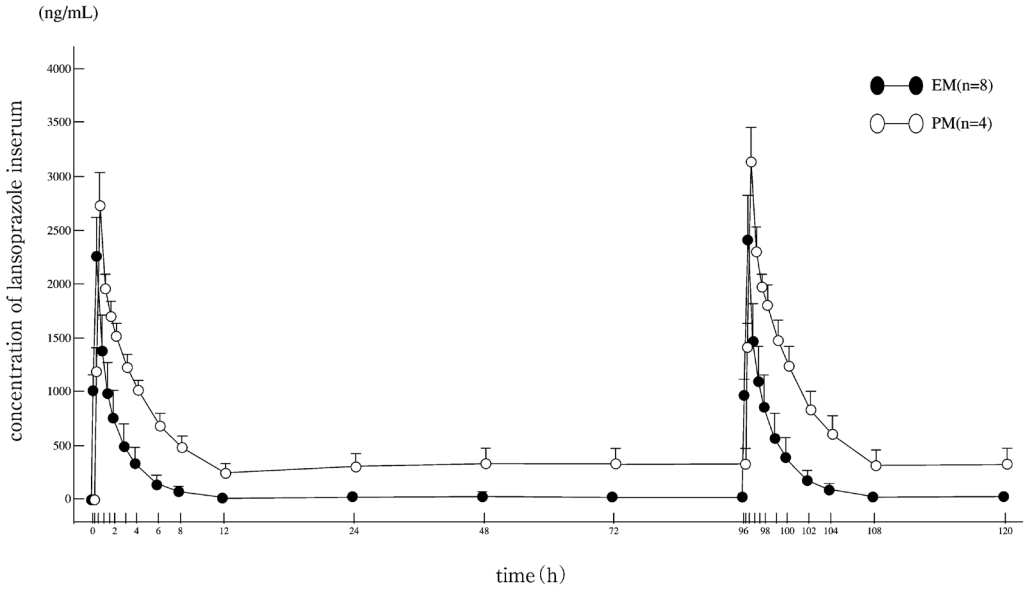
5.2 Pharmacokinetic properties

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)	Cmax (ng/mL)	$t_{1/2}$ (h)
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%.

5.3 Nonclinical Safety Data

Juvenile Animal Studies:

Five juvenile animal studies were conducted with lansoprazole which revealed no treatment related differences between juvenile and adult animals.

During a further 8-week juvenile rat study, cardiac valve thickening occurred at approximately 11-fold the expected human exposure, based on AUC. The findings reversed or trended towards reversibility after a 4-week drug-free recovery period. In a follow-up lansoprazole developmental sensitivity study, juvenile rats younger than postnatal Day 21 (age equivalent to approximately 2 years in humans) were more sensitive to the development of heart valve thickening, with valve thickening occurring at lower exposure (approximately 4-fold the expected human exposure based on AUC) in animals dosed starting at postnatal Day 14 (age equivalent to approximately 1 year in humans).

6 Pharmaceutical Particulars

6.1 List of excipients

Each vial of injection contains the excipients : mannitol, meglumine and sodium hydroxide.

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

Use within 4 hours in 5% glucose injection and 8 hours in isotonic sodium chloride solution after reconstitution.

6.5 Nature and contents of container

Box contains 1 vial @ 30 mg

REGISTRATION NO.
DKI1070700944A1

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

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