SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PREVACID®I.V. 30 mg for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 30 mg of lansoprazole

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to yellowish-white mass or powder.

pH: 10.6-11.3 (when dissolved in 5 mL of isotonic sodium chloride solution [JP]).

Osmotic pressure ratio: approximately 1*

*When dissolved in 5 mL of isotonic sodium chloride solution [JP].

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Patients with the following diseases who are unable to take the oral formulation:
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, one vial of PREVACID®I.V. (Lansoprazole 30 mg) is mixed with isotonic sodium chloride solution (NSS) or 5% dextrose in water (D5W) and administered by intravenous injection or intravenous drip twice a day; with the following directions.

1. Intravenous injection

Use 5 – 10ml NSS or D5W to mix with PREVACID®I.V., shake the vial gently until getting clear and colorless solution. Then draw all solution back and gently inject intravenously over 2 minutes.

2. Intravenous drip

2.1 Use 5 – 10ml NSS or D5W to mix with PREVACID®I.V., shake the vial gently until getting clear and colorless solution.

2.2 Then draw all solution back and mix with NSS or D5W 100 ml and then administer by intravenous drip as follows.

Mixing with NSS, drip the solution within 12 hours

Mixing with D5W, drip the solution within 5 hours

Special populations

Use in hepatic disorder

A delay in the metabolism and excretion of PREVACID® I.V. 30 mg may occur

Use in elderly

Since physiological function is generally decreased in elderly patients, *PREVACID®I.V.* should be carefully administered. The gastric acid secretion in general and other physiological functions are decreased in elderly patients

Use in children

The safety of *PREVACID®I.V.* in children has not been established (no clinical experience).

4.3 Contraindications

PREVACID®I.V. 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 or rilpivirine hydrochloride (See 4.5 Interaction with other medicinal products and other forms of interactions).

4.4 Special warnings and precautions for use

1. **Careful Administration** (*PREVACID®I.V.* 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 *PREVACID®I.V.* may occur.)
   (3) Elderly patients (see **USE IN THE ELDERLY**)
2. **Important Precautions**
   (1) As *PREVACID®I.V.* 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 (See **CLINICAL STUDIES**).
   (2) There is no clinical experience of treatment over 7 days in Japanese clinical trials.
   (3) 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 *PREVACID®I.V.* is ineffective, it should be switched to another treatment.
   (4) 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.
3. **Other Precautions**
   (1) 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 testicularinterstitial 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.
   (2) The administration of *PREVACID®I.V.* 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.

(3) In several observational studies in overseas, an increased risk for osteoporosis-related fractures of the hip, wrist or spine under the treatment with proton pump inhibitors has been reported. The risk of fracture was especially increased in the patients receiving high dose or long term (a year or longer) treatment.

(4) In several overseas observational studies, mainly in hospitalized patients, increased risk of gastrointestinal infection caused by *Clostridium difficile* was reported in patients who received proton pump inhibitors.

(5) Cyanocobalamin (Vitamin B-12) Deficiency: Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than three years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

4.5 Interaction with other medicinal products and other forms of interaction

PREVACID®I.V. is metabolized mainly by hepatic drug-metabolizing enzyme CYP2C19 and CYP3A4. Gastric antisecretory effect of *PREVACID®I.V.* may promote or inhibit absorption of concomitant drugs.

(1) **Contraindications for coadministration**
(*PREVACID®I.V.* 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 *PREVACID®I.V.* may reduce solubility of atazanavir sulfate, resulting in a decrease in the blood concentration of atazanavir.
Rilpivirine hydrochloride (Edurant)	Effect of rilpivirine hydrochloride may be diminished.	Gastric antisecretory effect of *PREVACID®I.V.* may reduce absorption of rilpivirine hydrochloride, resulting in a decrease in the blood concentration of rilpivirine.

(2) **Precautions for coadministration** (*PREVACID®I.V.* 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.	*PREVACID®I.V.* 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.	*PREVACID®I.V.* 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 *PREVACID®I.V.* may inhibit hydrolysis of digoxin, resulting in an increase in the blood concentration of digoxin.
Itraconazole Tyrosine Kinase Inhibitors Gefitinib Bosutinib Hydrate Nilotinib Hydrochloride Hydrate Erlotinib Hydrochloride Acalabrutinib Ceritinib Dasatinib Hydrate Dacomitinib Hydrate Lapatinib Tosilate Hydrate Capmatinib Hydrochloride Hydrate	Effects of these drugs may be diminished. Avoid coadministration of Bosutinib Hydrate as far as possible.	Gastric antisecretory effect of *PREVACID®I.V.* may lead to a decrease in the blood concentration of these drugs.
Magnesium oxide	The laxative effect of magnesium oxide may be diminished.	Lansoprazole is considered to increase the gastric pH and decrease the solubility of magnesium oxide.
Methotrexate	An increase in the concentration of methotrexate in blood may occur. In high-dose methotrexate administration, a temporary withdrawal of *PREVACID®I.V.* should be considered.	The mechanism is unknown.
Phenytoin Diazepam	Effects of these drugs may be enhanced	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.

4.6 Fertility, pregnancy and lactation

(1) PREVACID®I.V. 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 PREVACID®I.V. 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

There is no available information.

4.8 Undesirable effects

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%). (At the time of approval)

Adverse reactions, including abnormalities in laboratory data, were observed in 35 (3.1%) of 1,142 patients in the postmarketing investigations. The major adverse reactions were diarrhea, hepatic dysfunction, hepatic disorder, fever and leukocyte count decreased (0.3% each). (As of the end of the reexamination)

(1) Clinically significant adverse reactions (All frequencies unknown)

1) **Anaphylactic reactions** (generalized rash, facial edema, dyspnea, etc.) may occur, and shock has consequently occurred in certain cases. Therefore, close observation should be made, and if any abnormality is observed, *PREVACID®I.V.* should be discontinued and appropriate measures taken.
2) **Pancytopenia, agranulocytosis or hemolytic anemia may occur**. **Granulocytopenia, thrombocytopenia or anemia may occur**. Therefore, close observation should be made, and if any abnormality is observed, such appropriate measures as discontinuation of *PREVACID®I.V.* should be taken.
3) **Severe hepatic dysfunction** with jaundice, increased AST(GOT), ALT(GPT), etc., may occur. Therefore, close observation should be made. If any abnormality is observed, *PREVACID®I.V.* should be discontinued and appropriate measures taken.

4) **Toxic epidermal necrolysis: TEN** and **oculomucocutaneous syndrome** (Stevens-Johnson syndrome) may occur. Therefore, close observation should be made. If any abnormality is observed, *PREVACID®I.V.* should be discontinued and appropriate measures taken.
5) **Interstitial pneumonia** 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 *PREVACID®I.V.* should be discontinued. Appropriate measures, such as treatment with a corticosteroid preparation, should be taken.
6) **Tubulointerstitial nephritis** 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, *PREVACID®I.V.* should be discontinued and appropriate measures taken.

(2) Clinically significant adverse reactions (similar drug)

The following adverse reactions are reported in a similar drug (Omeprazole)

Visual disturbance may occur. Therefore, if any abnormality is observed, *PREVACID®I.V.* should be discontinued and appropriate measures taken

(3) Other adverse reactions

	5% ≤	0.1%-<5%	<0.1%	Frequency unknown
1) Hypersensitivity		Rash note2)		Pruritus, or erythema multiforme
2) Skin				Subacute cutaneous lupus erythematosus
3) Hepatic	Increased AST(GOT) or ALT(GPT)	Increased AL-P, LDH, or γ-GTP		
4) Hematologic		Eosinophilia		
5) Gastrointestinal		diarrhea	Constipation note2) or taste abnormality note2)	Thirst, feeling of enlarged abdomen, nausea, vomiting, anorexia, abdominal pain, candidiasis, stomatitis, glossitis, or colitis (including collagenous colitis etc. note1)
6)		Insomnia note2) or	Depressed	Headache, sleepiness or

Psychoneurologic		tremor	state[note2)]	dizziness
7) Others		Fever, or increased uric acid	Weakness[note2)]	Gynecomastia, edema, malaise, numbness of tongue or lips, numbness of limbs, muscle pain, alopecia, blurred vision, arthralgia, hyponatraemia, hypomagnesemia, hypokalemia, hypocalcemia or increased total cholesterol

*Note1) If diarrhea persists, there is a possibility that the patient developed collagenous colitis etc,. Therefore, *PREVACID® I.V.* should be promptly discontinued. Since abnormalities, such as longitudinal ulcers, erosion or easy bleeding, may be observed in intestinal submucosa, appropriate measures should be taken when melaena or bloody stool is observed.

*Note2) Frequency rates were based on the results of the postmarketing investigation.

4.9 Overdose

There is no available information.

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.

Clinical efficacy and safety

In clinical trials of *PREVACID®I.V.* in patients with peptic ulcer accompanied by bleeding etc., those in whom hemostasis was observed within 3 days (72 hours) accounted for 94.6% (192/203 patients) of 203 patients who had been evaluated for the hemostatic effect after intravenous administration of 30 mg of this drug twice a day. Of the 203 patients, 41 did not undergo endoscopic pretreatment, while 97.6% of these patients (40/41) had successful hemostasis within 3 days (72 hours).

The frequency of adverse reactions was 14.0% (31/221) and the major adverse reactions were ALT increase 6.2% (13/211), AST increase 5.7% (12/212) and γ-GTP increase 1.5% (3/195).

The frequency of adverse events by background factors of patients were 21.8% (12/55 patients) in females, 33.9% (19/56) in the elderly, and 29.7% (11/37) in patients with body weight of less than 50.0 kg, indicating slightly higher incidences, respectively, compared with 12.7% (21/166) in males, 8.5% (14/165) in the non-elderly, and 14.9% (11/74) in patients with body weight of 50.0 kg or over but less than 60.0 kg, or 10.0% (10/100) in patients with body weight of 60.0 kg or over (excluding those with unknown body weight).

5.2 Pharmacokinetic properties

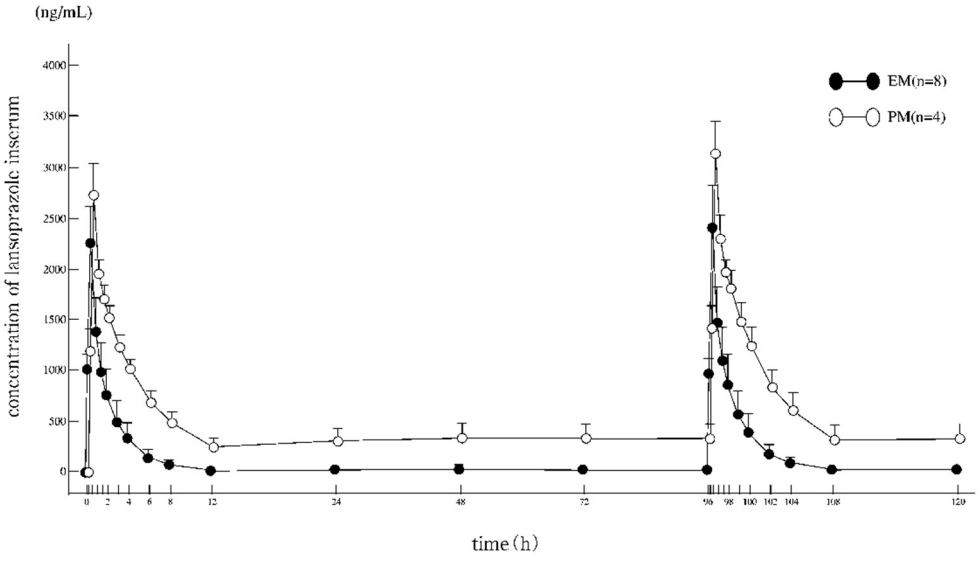
Blood concentrations

The serum concentration of lansoprazole after intravenous administration of *PREVACID®I.V.* 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 .

Serum concentration of lansoprazole

	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



Serum concentration-time profile (Mean+S.D.)

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% (*in vitro*).

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 Preclinical safety data

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 animal3). 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-mannitol
Meglumine
Sodium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

See on carton package

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 30 mg powder

Pack of 1 vial

6.6 Special precautions for disposal and other handling

Precautions concerning Use

(1) Route of administration: A dedicated infusion line should be used for the administration of PREVACID®I.V. Intravenous 30 mg. The infusion line should not be shared with other drugs. If it is inevitable to administer PREVACID®I.V. Intravenous 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 (JP) before and after administration of PREVACID®I.V. Intravenous 30 mg.

(2) After dissolution:
PREVACID®I.V. should be used immediately after dissolution and the dissolved solution should not be stored since the solution may deteriorate over time.
Mixing with NSS, drip the solution within 12 hours
Mixing with D5W, drip the solution within 5 hours

(3) Incompatibility:
Combined injection of PREVACID®I.V. with solutions other than isotonic sodium chloride solution or 5% glucose (dextrose) injection such as infusion fluid, replacement fluid, and other drugs should be avoided

7 Marketing authorization holder

Manufactured by: MOCHIDA PHARMACEUTICAL PLANT CO., LTD. Tochigi, Japan
(for TAKEDA PHARMACEUTICAL COMPANY LIMITED, Osaka, Japan)

Imported by: Takeda (Thailand), Ltd. Bangkok, Thailand

8 Marketing authorization Numbers

Reg.No. 1C 4/53 (N)

9 Date of authorization

28 Dec 2012

10 Date of revision of the text

April 2024