

Revised: February 2009 (9th version)

Standard Commodity Classification No. of Japan
872171

- Drug for Ischemic heart disease -
- Isosorbide dinitrate tablets, JP -

Nitorol[®] Tablets 5 mg

<Isosorbide dinitrate>

Prescription drug

Storage
NITOROL should be stored at room temperature. The bottle package should be stored in airtight condition and protected from moisture after opening cap.

Approval No.	21900AMX00011000
Date of listing in the NHI reimbursement price	Feb 1978
Date of initial marketing in Japan	Jan 1963
Date of latest reexamination	Mar 1998

Expiration date
NITOROL should be used before the expiration date indicated on the package or label.

Caution: See "PRECAUTIONS FOR HANDLING" section.

Caution : Use only as directed by a physician.

CONTRAINDICATIONS (NITOROL is contraindicated in the following patients.)

1. Patients with serious hypotension or cardiogenic shock
[NITOROL may lower blood pressure and aggravate symptoms due to its vasodilative action.]
2. Patients with closed angle glaucoma
[NITOROL may increase intraocular pressure.]
3. Patients with a head injury or cerebral hemorrhage
[NITOROL may increase intracranial pressure.]
4. Patients with severe anemia
[Anemic symptoms (e.g. dizziness, dizziness on standing up) may be aggravated by a decrease in blood pressure.]
5. Patients with a history of hypersensitivity to nitrate or nitrite ester preparations.
6. Patients taking phosphodiesterase type 5 inhibitors (sildenafil citrate, vardenafil hydrochloride hydrate or tadalafil).
[Combination therapy potentiates the hypotensive action and may induce an excessive decrease in blood pressure. See "Drug Interactions" section.]

INDICATIONS

Angina pectoris, myocardial infarction and other ischemic heart diseases

DOSAGE AND ADMINISTRATION

Oral administration

The usual adult dosage for oral use is 1 to 2 tablets (5 to 10 mg of isosorbide dinitrate) three to four times daily. The dosage may be adjusted depending on the patient's age and symptoms.

Sublingual administration

At the time of an attack, the usual adult dosage for sublingual use is 1 to 2 tablets (5 to 10 mg of isosorbide dinitrate).

When the sublingual route is used for prophylaxis, the usual adult dosage for sublingual use is 1 to 2 tablets (5 to 10 mg of isosorbide dinitrate) three to four times daily. The dosage may be adjusted depending on the patient's age and symptoms.

DESCRIPTION

1. Composition

Each white plain tablet contains 5 mg of isosorbide dinitrate. It also contains carmellose calcium, microcrystalline cellulose, synthetic aluminium silicate, magnesium stearate, talc, corn starch, lactose hydrate and dibasic calcium phosphate hydrate as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
NITOROL Tablets 5 mg	Plain tablets				White
		Diameter (mm) 6.1	Weight (mg) 100	Thickness (mm) 2.6	

PRECAUTIONS

1. Careful Administration (NITOROL should be administered with care in the following patients.)

- (1) Patients with hypotension
[NITOROL may lower blood pressure due to its vasodilative action.]
- (2) Patients in the acute stages of myocardial infarction
[NITOROL may lower blood pressure.]
- (3) Patients with primary pulmonary hypertension
[NITOROL may decrease cardiac output and cause shock.]
- (4) Patients with hypertrophic obstructive cardiomyopathy
[NITOROL may increase the ventricular internal pressure gradient and aggravate symptoms.]

2. Important Precautions

- (1) If an **excessive decrease in blood pressure** occurs, treatment with NITOROL should be discontinued and appropriate measures, such as **raising the lower extremities or administering a vasopressor**, taken.
- (2) Since **orthostatic hypotension** may occur, patients should be cautioned during treatment.
- (3) Like other nitrate and nitrite ester preparations, NITOROL is likely to cause adverse reactions such as headache due to its vasodilator action on the initiation of treatment. These adverse reactions may cause a decrease in attention, concentration, reflex movements, and other functions. In the event of such changes, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.
- (4) Since combination therapy with NITOROL and phosphodiesterase type 5 inhibitors (sildenafil citrate, vardenafil hydrochloride hydrate or tadalafil) potentiates the hypotensive action and may induce an excessive decrease in blood pressure, it should be confirmed that such drugs have not been administered before treatment with NITOROL. During and after treatment with NITOROL, patients should be cautioned not to take these drugs.

3. Drug Interactions

- (1) **Contraindications for coadministration (NITOROL should not be coadministered with the following drugs.)**

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Phosphodiesterase type 5 inhibitors Sildenafil citrate (Viagra), Vardenafil hydrochloride hydrate (Levitra) Tadalafil (Cialis)	When coadministered with these products, the hypotensive action may be potentiated.	NITOROL increases the production of cGMP, and phosphodiesterase type 5 inhibitors inhibit the degradation of cGMP. Therefore, coadministration with this product potentiates the hypotensive action, due to the resulting increase in cGMP.

- (2) **Precaution for coadministration (NITOROL should be administered with care when coadministered with the following drugs.)**

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Alcohol	Decrease in blood pressure or other symptoms may occur. If an excessive decrease in blood pressure occurs, NITOROL should be reduced in dosage or discontinued and appropriate measures, such as administering a vasopressor, taken, if necessary.	Alcohol potentiates the vasodilative action.
Diuretics	Decrease in blood pressure or other symptoms may occur. If an excessive decrease in blood pressure occurs, NITOROL should be reduced in dosage or discontinued and appropriate measures, such as administering a vasopressor, taken, if necessary.	They potentiate the hypotensive action.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Vasodilators Nitrate and nitrite ester preparations	Headache, decrease in blood pressure or other symptoms may occur. If an excessive decrease in blood pressure occurs, NITOROL should be reduced in dosage or discontinued and appropriate measures, such as administering a vasopressor, taken, if necessary.	They potentiate the vasodilative action.

4. Adverse Reactions

Adverse reactions for oral administration were reported in 353 of 2,083 patients (16.95%). (Sum of clinical trials)

Adverse reactions for sublingual administration were reported in 43 of 958 patients (4.49%). (Sum of clinical trials)

	≥5%	5% > ≥0.1%	<0.1%	Incidence unknown
Cardiovascular		Dizziness, decrease in blood pressure, flushing and palpitations		Feeling of warmth and syncope
Psychoneurologic	Headache	Weakness		Feeling unwell
Hypersensitivity ^(note)			Rash	
Gastrointestinal		Nausea/vomiting, stomach discomfort and anorexia		
Hepatic				Elevation of AST (GOT) and ALT (GPT), etc.

Note) In the event of such symptoms, treatment should be discontinued.

5. Use in the Elderly

NITOROL is metabolized primarily in the liver. Since the elderly generally have a lowered liver function, they should be carefully observed to avoid the risk of a high blood concentration continuing. It is advisable that NITOROL is taken under careful supervision.

6. Use during Pregnancy, Delivery or Lactation

- (1) NITOROL should only be used for pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment.

[The safety of NITOROL during pregnancy has not been established.]

- (2) It is advisable to avoid administration to nursing mothers. When NITOROL must be used, breast feeding should be discontinued during treatment.

[It has been reported in an animal study (in rats) that NITOROL is excreted in breast milk.]

7. Precautions concerning Use

Caution in handing over drug

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

8. Other Precautions

(1) If NITOROL is used continuously, tolerance to it and cross tolerance to other nitrate and nitrite ester preparations may be developed, with the result that their efficacies are reduced.

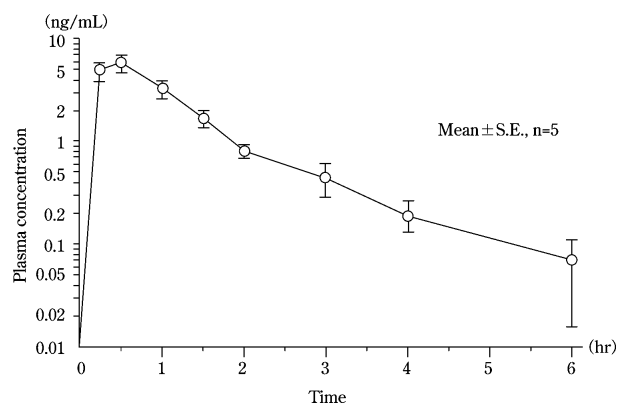
In controlled clinical trials conducted on effort angina outside of Japan, using transdermal preparations of an analog compound (nitroglycerin), it has been reported that an intermittent-dosing regimen could suppress reduction in tolerance.

(2) Methemoglobinemia has been reported in patients treated with an isosorbide dinitrate preparation.

PHARMACOKINETICS

1. Blood concentration

When 1 tablet of NITOROL (5 mg of isosorbide dinitrate) was administered orally to 5 healthy adult male volunteers in a single dose, the time to reach the peak plasma concentration ($C_{max} = 5.8$ ng/mL) was 25.6 min after administration. Thereafter, the plasma concentration decreased in a biphasic pattern with half-life at the α phase of 18.2 min and half-life at the β phase of 93.5 min. The plasma concentration had fallen to 0.07 ng/mL at 6 hr after administration. The area under the plasma concentration-time curve (AUC (0- ∞)) was 7.5 ng · hr/mL.



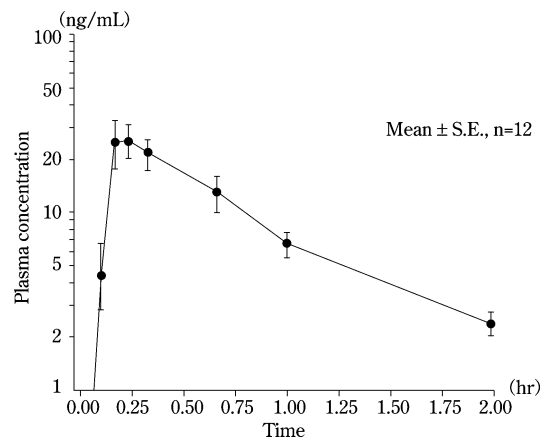
Changes in plasma isosorbide dinitrate concentration after oral administration of a NITOROL Tablets 5 mg

Pharmacokinetic parameters for oral administration of NITOROL Tablets 5 mg

C_{max} (ng/mL)	t_{max} (min)	AUC (ng·hr/mL)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)
5.8±0.7	25.6±4.9	7.5±1.3	18.2±1.4	93.5±20.0

(Mean±S. E., n=5)

When 1 tablet of NITOROL (5 mg of isosorbide dinitrate) was administered sublingually to 12 healthy adult male volunteers in a single dose, the time to reach the peak plasma concentration ($C_{max} = 35.7$ ng/mL) was 18.2 min after administration. Thereafter, the plasma concentration decreased in a biphasic pattern with a half-life at the α phase of 7.5 min and a half-life at the β phase of 55.2 min. AUC (0- ∞) was 21.0 ng · hr/mL. ¹⁾



Changes in plasma isosorbide dinitrate concentration after sublingual administration of a NITOROL Tablets 5 mg

Pharmacokinetic parameters for sublingual administration of NITOROL Tablets 5 mg

C_{max} (ng/mL)	t_{max} (min)	AUC (ng·hr/mL)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)
35.7±6.4	18.2±3.2	21.0±2.7	7.5	55.2

(Mean±S. E., n=12)

2. Urinary excretion

When 1 tablet of NITOROL (5 mg of isosorbide dinitrate) was administered orally to 5 healthy adult volunteers in a single dose, within the first 48 hr, 0.23% and 0.47% of the drug had been excreted as free isosorbide 2-mononitrate and its glucuronide, respectively, while 4.02% and 10.03% of the drug had been excreted as free isosorbide 5-mononitrate and its glucuronide, respectively.

CLINICAL STUDIES

Clinical efficacy

In open labeled clinical trials, NITOROL has been demonstrated to be useful in that it reduces the incidence of anginal attacks, and improves exercise tolerance and electrocardiograph parameters. ²⁻⁴⁾

PHARMACOLOGY

1. Reduction of cardiac preload and afterload

In anesthetized dogs, isosorbide dinitrate decreases venous return, pulmonary wedge pressure and left ventricular end-diastolic blood pressure (reduction of preload) based on dilating venous capacitance vessels. It also decreases total peripheral vascular resistance (reduction of afterload) by dilating peripheral arteries. All these effects contribute to a decrease in myocardial oxygen demands. ^{5,6)}

2. Vasodilation of coronary arteries

In anesthetized dogs, isosorbide dinitrate decreases coronary vascular resistance by dilating relatively thick coronary arteries (conductive vessels) and also dilates collateral vessels. Although the increase in coronary blood flow is slight, this contributes to the re-distribution of blood flow to ischemic myocardial areas, in particular in the lower layer of the intima, results in increases in myocardial oxygen supply. ⁷⁾

3. Production of cyclic GMP (cGMP)

When isosorbide dinitrate is added to isolated calf coronary artery previously contracted with potassium chloride, production of cGMP increases in proportion to the degree of relaxation of the coronary artery.⁸⁾

PHYSICOCHEMISTRY

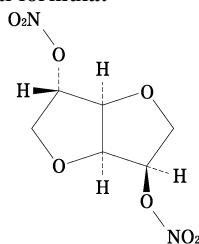
Nonproprietary name: Isosorbide Dinitrate (JAN, INN)

Chemical name: 1,4:3,6-Dianhydro-D-glucitol dinitrate

Molecular formula: C₆H₈N₂O₈

Molecular weight: 236.14

Structural formula:



Description:

Isosorbide Dinitrate occurs as white crystals or crystalline powder. It is odorless or has a faint odor like that of nitric acid.

It is very soluble in *N, N*-dimethylformamide and in acetone, freely soluble in chloroform and in toluene, soluble in methanol, in ethanol (95) and in diethyl ether, and practically insoluble in water.

It explodes if heated quickly or subjected to percussion.

PRECAUTIONS FOR HANDLING

1. When NITOROL is stored in a high temperature or high-humidity environment for a long time, crystallines may form on the surface of the tablets.
2. Not to leave NITOROL tablets in an auto packaging machine, because the NITOROL contents diminution had been shown under the open aired condition. It also should be avoided chronic administration with divided bag.
3. NITOROL tablets should be stored in cool condition after divided in bag.

PACKAGING

Isosorbide Dinitrate Tablets, JP

NITOROL Tablets 5 mg:

Boxes of 100 and 1,000 in press through packages, and bottles of 500

REFERENCES

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- 4) Haraoka S. et al.: Shinryo, **18**, 521, 1965.
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- 6) Wendt R.L.: J. Pharmacol. Exp. Ther., **180**, 732, 1972.
- 7) Takayama Y. et al.: J. Jpn. Coll. Angiol., **21**, 351, 1981.
- 8) Matrib M.A. et al.: Am. Heart J., **110**, 204, 1985.

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Customer Information Services Section

Free Dial: 0120-419-497

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BRAND NAMES IN OTHER COUNTRIES

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