

Revised: November 2007 (9th version)

Standard Commodity Classification No. of Japan
872171

- Long-acting isosorbide dinitrate preparation -  
**Nitorol® R Capsules 20mg**

&lt;Isosorbide dinitrate preparation&gt;

Prescription drug

Storage
NITOROL R should be stored at room temperature.

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

Approval No.	15700AMY00074000
Date of listing in the NHI reimbursement price	Aug 1982
Date of initial marketing in Japan	Aug 1982
Date of latest reexamination	Dec 1986
Date of latest reevaluation	Mar 1998

Caution : Use only as directed by a physician.

**CONTRAINDICATIONS (NITOROL R is contraindicated in the following patients.)**

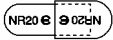
- Patients with serious hypotension or cardiogenic shock  
[NITOROL R may lower blood pressure and aggravate symptoms due to its vasodilator action.]
- Patients with closed angle glaucoma  
[NITOROL R may increase intraocular pressure.]
- Patients with a head injury or cerebral hemorrhage  
[NITOROL R may increase intracranial pressure.]
- Patients with severe anemia  
[Anemic symptoms (e.g. dizziness, dizziness on standing up) may be aggravated by a decrease in blood pressure.]
- Patients with a history of hypersensitivity to nitrate or nitrite ester preparations.
- 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.]

**DESCRIPTION****1. Composition**

Each white, hard capsule contains 20 mg of isosorbide dinitrate.

It also contains ethylcellulose, purified shellac, gelatin, talc, corn starch, lactose hydrate, white soft sugar, and sodium lauryl sulfate as inactive ingredients.

**2. Product description**

Brand name	Dosage form and identification code	Appearance			Description
NITOROL R Capsules 20 mg	Hard capsules				Capsule Cap: white Body: white Contents: white to light yellow, sustained-release granules
	NR20E	Diameter (mm) 14.0	Weight (mg) 209	Size No.4	

**INDICATIONS**

Angina pectoris, myocardial infarction (excluding acute phase) and other ischemic heart diseases

**<Precautions>**

NITOROL R is not a suitable drug for therapy aimed at relieving anginal attacks. For the purpose of relief of attacks, rapid-acting nitrate or nitrite ester preparations should be used.

**DOSAGE AND ADMINISTRATION**

The usual adult dosage for oral use is one capsule (20 mg of isosorbide dinitrate) twice daily.

The dose should be adjusted depending on the patient's age and symptoms.

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

- Patients with hypotension  
[NITOROL R may lower blood pressure due to its vasodilative action.]
- Patients with primary pulmonary hypertension  
[NITOROL R may decrease cardiac output and cause shock.]
- Patients with hypertrophic obstructive cardiomyopathy  
[NITOROL R may increase the ventricular internal pressure gradient and aggravate symptoms.]
- Patients with hepatic function disorder  
[Since high blood concentrations may continue, such measures as reduction in dosage should be taken.]
- The elderly [see "Use in the Elderly" section.]

**2. Important Precautions**

- Patients taking NITOROL R should be carefully observed for symptoms and course of disease. NITOROL R should be switched to other treatment when there is a lack of a satisfactory clinical response as indicated by aggravation of the anginal attacks.
- If an excessive decrease in blood pressure occurs, treatment with NITOROL R should be discontinued,

and appropriate measures, such as **raising the lower extremities or administration of a vasopressor**, taken.

- (3) It has been reported that sudden withdrawal of nitrate or nitrite ester preparations resulted in the aggravation of symptoms. When NITOROL R is to be withdrawn, **it should be tapered off while being concomitantly administered with an alternative drug**. The patient should be warned against discontinuing NITOROL R without the instruction of their attending physician.
- (4) Since **orthostatic hypotension** may occur, patients should be made aware of this during treatment.
- (5) Like other nitrate and nitrite ester preparations, NITOROL R may cause adverse reactions such as headache due to its vasodilator action on the initiation of treatment. In the event of such symptoms, appropriate measures, such as administration of analgesics or reduction in dosage or discontinuation of the medication, should be taken. These adverse reactions may cause a decrease in attention, concentration, reflex movement or other functions. In the event of any such changes, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.
- (6) 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 R 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 this product, the hypotensive action may be potentiated.	NITOROL R 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) Precautions for coadministration (NITOROL R 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 R should be reduced in dosage or discontinued and appropriate measures, such as administering a vasopressor taken, if necessary.	Alcohol potentiates the vasodilative action.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Diuretics	Decrease in blood pressure or other symptoms may occur. If an excessive decrease in blood pressure occurs, NITOROL R should be reduced in dosage or discontinued and appropriate measures, such as administering a vasopressor taken, if necessary.	They potentiate the hypotensive action.
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 R 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 were reported in 463 of 10,098 patients (4.59%). (At the end of the reexamination period)

	5% > ≥0.1%	<0.1%	Incidence unknown
Cardiovascular	Dizziness, light headedness, feeling of warmth, flushing and palpitations	Edema and decrease in blood pressure	
psychoneurologic	Headache and dull headache	Generalized fatigability and tinnitus	Weakness and feeling unwell
Gastrointestinal	Nausea/vomiting, stomach discomfort and upper abdominal pain	Anorexia	
Hepatic		Elevation of AST (GOT) and ALT (GPT), etc.	
Hypersensitivity <sup>note)</sup>		Rash	

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

### 5. Use in the Elderly

NITOROL R 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 R is taken under careful supervision.

### 6. Use during Pregnancy, Delivery or Lactation

- (1) NITOROL R 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 R during pregnancy has not been established.]
- (2) It is advisable to avoid administration to nursing mothers. When NITOROL R must be used, breast feeding should be discontinued during treatment.  
[It has been reported in an animal study (rats) that NITOROL R is excreted in breast milk.]

### 7. Pediatric Use

The safety in children has not been established (insufficient clinical experience).

## 8. Precautions concerning Use

### (1) Oral administration

The patient should be instructed not to bite or chew the capsules, but to swallow them. If the capsule is crushed, the drug concentration in the blood may increase temporarily which is likely to cause a headache.

### (2) 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.]

## 9. Other Precautions

(1) If NITOROL R 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 tolerance.

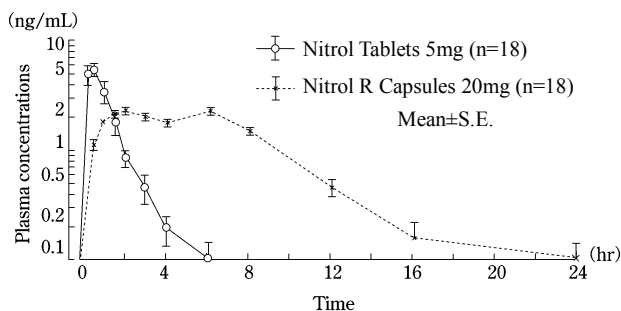
(2) Methemoglobinemia has been reported in patients treated with isosorbide dinitrate.

## PHARMACOKINETICS

### 1. Blood concentrations

The stable plasma concentrations (about 2.0 ng/mL) were maintained over 1 to 6 hr after oral administration of one NITOROL R capsule (20 mg of isosorbide dinitrate) to 18 healthy adult male volunteers. Plasma concentrations of about 0.4 ng/mL were maintained at 12 hr after administration. When a conventional Isosorbide dinitrate Tablets (5 mg) was administered orally, the peak plasma concentrations (5.8 ng/mL) was reached 25.6 min after administration and decreased to 0.07 ng/mL at 6 hr after administration.

NITOROL R was thus found to maintain plasma concentrations of 0.4 ng/mL and over for about 4 times as long as the conventional Isosorbide dinitrate Tablets.



Changes in plasma isosorbide dinitrate concentrations after oral administration of a NITOROL R Capsules 20 mg and a conventional Isosorbide dinitrate Tablets 5 mg

## Pharmacokinetic parameters after single administration of NITOROL R Capsules 20 mg

$C_{max}$ (ng/mL)	$t_{max}$ (hr)	$AUC_0^{24}$ (ng · hr/mL)
$2.7 \pm 0.14$	$3.5 \pm 0.50$	$21.0 \pm 1.63$

(Mean  $\pm$  S.E., n=18)

## 2. Relationship between plasma concentration and clinical efficacy

The plasma concentrations reached 1.9 ng/mL at 1 hr after oral administration of one NITOROL R capsule (20 mg of isosorbide dinitrate) to 5 patients with angina pectoris or myocardial infarction. Coronary arteriography conducted at this time point showed a mean expansion of the coronary diameter by about 19%. The mean plasma concentration remained at 2.36 ng/mL between 1 to 8 hr after administration. It was still at 2.0 ng/mL even 8 hr after administration. Pulmonary end-diastolic blood pressure decreased significantly at 6 and 8 hr after administration ( $p < 0.05$ ).<sup>1)</sup>

## CLINICAL STUDIES

### Clinical efficacy

- In double blind and open labeled clinical trials, NITOROL R was effective in 63.1% (321/509) of patients with ischemic heart diseases (effort angina, effort and rest angina, rest angina, myocardial infarction, etc.) treated with one capsule twice daily.<sup>2-7)</sup>
- In double blind and open labeled clinical trials conducted in patients with angina pectoris, the number of the attacks decreased significantly by about 1/2 in 2 weeks after administration.

The requirement for symptomatic doses of nitrite also decreased significantly by about 1/3 to 1/2.<sup>2,3,6,7)</sup>

## 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.<sup>8,9)</sup>

### 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.<sup>10)</sup>

### 3. Production of cyclic GMP (cGMP)

When isosorbide dinitrate is added to isolated calf coronary artery previously contracted using potassium chloride, production of cGMP increases in proportion to the degree of relaxation of the coronary artery.<sup>11)</sup>

## PHYSICOCHEMISTRY

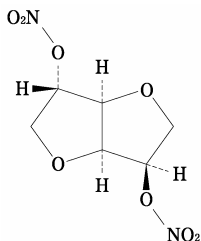
**Nonproprietary name:** Isosorbide Dinitrate (JAN, INN)

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

**Molecular formula:** C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>O<sub>8</sub>

**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.

## PACKAGING

### NITOROL R Capsules 20 mg:

Boxes of 100, 140 (14 Caps. × 10), 700 (14 Caps. × 50) and 1,000 in press-through-packages, and bottles of 500

## REFERENCES

- 1) Inoue K. et al.: J. Med. Pharm. Sci., **9**, 247, 1983.
- 2) Maeda T. et al.: Jap. J. Clin. Exp. Med., **59**, 255, 1982.
- 3) Abe H. et al.: *ibid.*, **59**, 1622, 1982.
- 4) Kashiwagi M. et al.: J. New Remed. Clin., **29**, 1687, 1980.
- 5) Osamura Y. et al.: Med. Consult. New Remed., **17**, 2119, 1980.
- 6) Nakano T. et al.: J. New Remed. Clin., **34**, 1441, 1985.
- 7) Furukawa I. et al.: Jap. J. Clin. Exp. Med., **63**, 2047, 1986.
- 8) Hirakawa S. et al.: Saishin Igaku, **29**, 170, 1974.
- 9) Wendt R.L.: J. Pharmacol. Exp. Ther., **180**, 732, 1972.
- 10) Takayama Y. et al.: J. Jpn. Coll. Angiol., **21**, 351, 1981.
- 11) Matlib M. A. et al.: Am. Heart J., **110**, 204, 1985.

### REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department

Fax: 03-3811-2710

Eisai Co., Ltd.

### REQUEST FOR PRODUCT INFORMATION SHOULD BE MADE TO:

Customer Information Service

Free Dial: 0120-419-497

Eisai Co., Ltd.

### Manufactured and marketed by:

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