Revised: June 2017 (14th version, Change of trade name)
Revised: July 2014 (13th version)

Therapeutic Agent for Ischemic Heart Disease

Prescription-only drug*1)

ISOSORBIDE DINITRATE SR TABLETS 20 mg "TOWA"

(Isosorbide Dinitrate sustained-release Tablet)

Storage:
Store at room temperature.

Expiration date:
Indicated on the package and label

Standard Commodity Classification No. of Japan 872171	
Approval No.	22900AMX00100
Date of listing in the NHI reimbursement price	June 2017
Date of initial marketing in Japan	July 1992
Date of result of reevaluation	March 1998
Date of reevaluation (quality)	September 2003

*1)Caution – Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (Isosorbide Dinitrate SR Tablets is contraindicated in the following patients.)

1) Patients with serious hypotension or cardiogenic shock [The vasodilating effect of isosorbide dinitrate may further decrease blood pressure, leading to aggravated symptoms.]
2) Patients with angle closure glaucoma [Intraocular pressure may increase.]
3) Patients with head injury or cerebral hemorrhage [Intracranial pressure may increase.]
4) Patients with severe anemia [Decreased blood pressure may occur, leading to aggravated symptoms of anemia (e.g., dizziness and dizziness on standing up).]
5) Patients with a history of hypersensitivity to nitric/nitrous acid esters
6) Patients receiving phosphodiesterase type 5 inhibitors (sildenafil citrate, vardenafil hydrochloride hydrate, and tadalafil) or a soluble guanylate cyclase stimulator (riociguat) [Coadministration of this product and these drugs may increase the antihypertensive effects of these drugs, resulting in excessively decreased blood pressure (see "Drug Interactions").]

DESCRIPTION

Active ingredient per tablet	Isosorbide Dinitrate (JP) ····· 20mg		
Inactive ingredient	Lactose Hydrate, Corn Starch, Carnauba Wax, Hydrogenated Oil, Ethyl Cellulose, Hydroxypropylcellulose, Microcrystalline Cellulose, Talc, Magnesium Stearate, Light Anhydrous Silicic Acid		
Product description	White uncoated tablets with pale gray to light yellow irregular spots (Sustained tablets). It has a slight, characteristic odor.		
Identification code	Tablet	TwD.L	
	Package	Tw. D.L	
Appearance	Top surface	Bottom surface	Side surface
			
Diameter (mm)	8.0		
Thickness (mm)	3.5		
Weight (mg)	190		

INDICATION

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

PRECAUTIONS FOR INDICATIONS

This product is **not indicated for the remission of anginal attacks**; thus, rapid-acting nitric/nitrous acid esters should be used for anginal attack remission.

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 1 tablet (20 mg of isosorbide dinitrate) at a time, twice daily. The dosage may be adjusted according to the patient's age and symptoms. Take a tablet without chewing.

PRECAUTIONS

1. Careful Administration

(**Isosorbide Dinitrate SR Tablets** should be administered with care in the following patients.)

1) Patients with hypotension [The vasodilating effect of isosorbide dinitrate may further decrease blood pressure.]
2) Patients with primary pulmonary hypertension [Decreased cardiac output may occur, leading to shock.]
3) Patients with hypertrophic obstructive cardiomyopathy [Increased intraventricular pressure gradients may be observed, leading to aggravated symptoms.]
4) Patients with hepatic disorder [Increased blood isosorbide dinitrate concentrations may persist; thus, this product should be administered, along with dosage modification (e.g., dosage reduction).]
5) Elderly patients [See "Use in the Elderly".]

2. Important Precautions

1) During isosorbide dinitrate therapy, individual patients' symptoms and clinical course should be closely monitored. If no response to treatment (e.g., aggravation of anginal attacks) is observed, this therapy should be discontinued and replaced by other therapies.
2) It has been reported that, in patients receiving nitric/nitrous acid esters, aggravated symptoms were observed when these drugs were abruptly discontinued; **if administration must be suspended, dosage reduction should be performed in decrements along with coadministration with other drugs.**

In addition, caution should be exercised so that patients do not stop taking isosorbide dinitrate without the direction of a physician.

3) If **excessively decreased blood pressure** is observed, administration of this product should be discontinued and appropriate measures should be taken, including **leg raising and vasopressor administration**.
4) **Orthostatic hypotension** may occur; thus, caution should be exercised.
5) At the start of treatment of this product, adverse reactions such as headaches may be induced by the vasodilating effect of this product as well as of other nitric/nitrous acid esters. In such cases, appropriate measures should be taken, including analgesic drug administration and dosage reduction or discontinuation of isosorbide dinitrate. Furthermore, decreases in attentiveness, mental concentration, or reflex movements may occur due to such adverse reactions, in which cases patients should be cautioned against being engaged in the operation of machinery involving risks (e.g., driving a vehicle).
6) Coadministration of this product with phosphodiesterase type 5 inhibitors (sildenafil citrate, vardenafil hydrochloride hydrate, and tadalafil) or a soluble guanylate cyclase stimulator (riociguat) may induce increased antihypertensive effects of these drugs; this product should be administered after thorough confirmation of the absence of oral administration of these drugs. Careful attention should be paid to prevent patients from taking these drugs during or after isosorbide dinitrate therapy.

3. Drug Interactions

1) Contraindications for coadministration
(Isosorbide Dinitrate SR Tablets should not be administered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Phosphodiesterase type 5 inhibitors Sildenafil citrate Viagra Revatio Vardenafil Hydrochloride hydrate Levitra Tadalafil Cialis Adcirca Zalutia	Coadministration of isosorbide dinitrate with such drugs may increase the antihypertensive effect of this product.	This product facilitates the production of cyclic guanosine monophosphate (cGMP), while phosphodiesterase type 5 inhibitors inhibit the degradation of cGMP; thus, coadministration of isosorbide dinitrate with these inhibitors may lead to increased cGMP, thereby increasing the antihypertensive effect of this product.
Soluble guanylate cyclase stimulators Riociguat Adempas		Both this product and soluble guanylate cyclase stimulators facilitate cGMP production; thus, coadministration of isosorbide dinitrate with these stimulators may lead to increased cGMP, thereby increasing the antihypertensive effect of this product.

2) **Precautions for Coadministration (Isosorbide Dinitrate SR Tablets should be administered with care when coadministered with the following drugs.)**
Appropriate measures (e.g., drug dosage reduction or discontinuation, and leg raising or vasopressor administration) should be taken if excessively decreased blood pressure occurs due to interactions between isosorbide dinitrate and any of the following:

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Alcohol intake	Such symptoms as decreased blood pressure may increase in frequency and severity.	The vasodilating effect of isosorbide dinitrate may be increased.
Diuretics	Such symptoms as decreased blood pressure may increase in frequency and severity.	The blood pressure-lowering effect of isosorbide dinitrate may be increased.
Vasodilators Nitric/nitrous acid esters	Adverse reactions including headaches and decreased blood pressure may increase in frequency and severity.	The vasodilating effect of isosorbide dinitrate may be increased.

4. Adverse Reactions

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

	Incidence unknown
Cardiovascular	Dizziness/wamble, feeling of warmth, flushing, palpitations, decreased blood pressure, edema
Psychoneurologic	Headache, heaviness of head, tinnitus, general malaise, weakness, discomfort
Hypersensitivity*2)	Rash
Gastrointestinal	Nausea/vomiting, stomach discomfort, upper abdominal pain, anorexia
Hepatic	Increased AST(GOT), increased ALT(GPT), etc.

*2): Administration of this product should be discontinued.

5. Use in the Elderly

This product is metabolized primarily in the liver. Since the elderly generally have decreased hepatic function, increased isosorbide dinitrate concentrations may persist in elderly patients. Thus, caution should be exercised.

6. Use during Pregnancy, Delivery or Lactation

1) This product should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established.]
2) Administration of this product to lactating mothers is not recommended. If use of this product is judged to be essential, breast feeding must be discontinued during treatment. [Animal studies (in rats) have shown that the drug is excreted in breast milk.]

7. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants and children has not been established.

8. Precautions Concerning Use

1) **Precautions regarding oral administration**:
If this product is swallowed after being crushed in the mouth, blood isosorbide dinitrate concentrations transiently increase and patients may be placed at increased risk of developing a headache. This product must be swallowed without being crushed in the mouth.
2) **Precautions regarding dispensing**:
For drugs that are dispensed in a PTP (press-through package) sheet, 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 severe complications such as mediastinitis.]

9. Other precautions

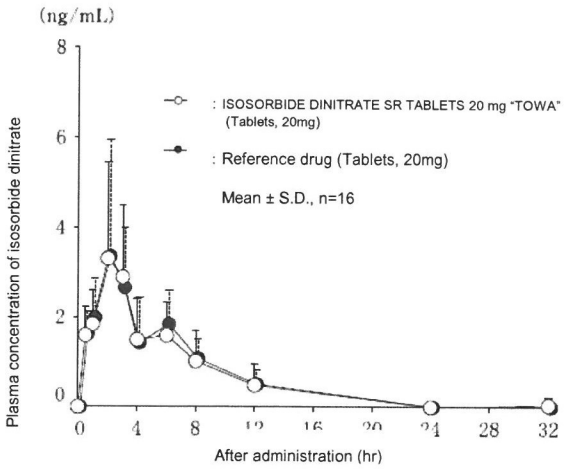
1) During treatment with this product, tolerance to this product or to other nitric/nitrous acid esters may develop and the effects of these drugs may decrease.
   In controlled clinical studies outside of Japan to investigate a transdermal formulation of an analogue (nitroglycerin) for angina on exercise, it has been reported that tolerance to nitroglycerin was mitigated by setting a wash-out period.
2) It has been reported that isosorbide dinitrate administration led to the onset of methemoglobinemia.

PHARMACOKINETICS

1. Bioequivalence test

One tablet each of ISOSORBIDE DINITRATE SR TABLETS 20mg "TOWA" and a reference drug (as 20 mg of isosorbide dinitrate) were administered orally as a single dose to healthy adult men under fasting conditions (n=16) and under fed conditions (n=16) in a crossover design to measure each unchanged drug concentration in plasma. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs (based on PAB/PCD Notification No. 718, May 30, 1980)[1].

(1) Administration under fasting conditions

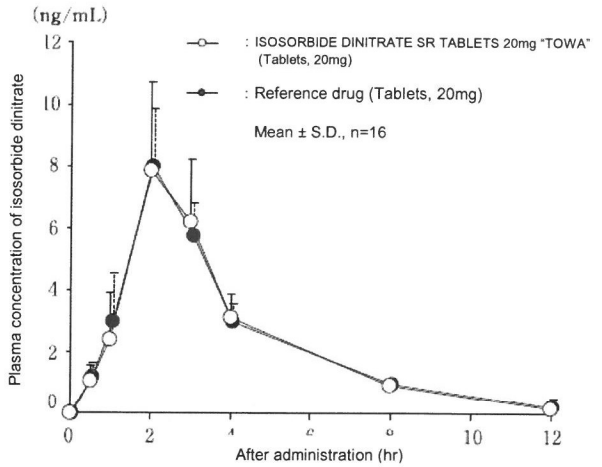


	Determined parameter		Reference parameter	
	AUC_{32} (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
ISOSORBIDE DINITRATE SR TABLETS 20mg "TOWA" (Tablets, 20mg)	20.95±9.46	3.83±2.09	2.8±1.5	5.6±3.1
Reference drug (Tablets, 20mg)	21.44±8.55	3.92±2.29	2.9±1.7	4.4±1.5

(Mean ± S.D., n=16)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

(2) Administration under fed conditions



	Determined parameter		Reference parameter	
	AUC_{12} (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
ISOSORBIDE DINITRATE SR TABLETS 20mg "TOWA" (Tablets, 20mg)	28.32±5.00	8.34±2.54	2.06±0.44	2.36±0.66
Reference drug (Tablets, 20mg)	28.32±3.67	8.17±1.65	1.94±0.25	2.32±0.49

(Mean ± S.D., n=16)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

(2) Administration under fed conditions

2. Dissolution profile

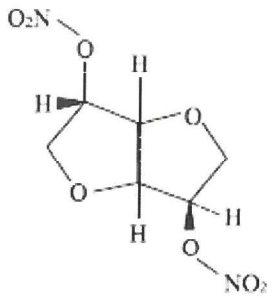
ISOSORBIDE DINITRATE SR TABLETS 20mg "TOWA" have been confirmed to conform to the corresponding dissolution standards of Isosorbide dinitrate Extended-release Tablets defined in the third section of the Japanese Pharmaceutical Codex[2].

PHARMACOLOGY

Consistent with nitroglycerin, isosorbide dinitrate releases nitric oxide (NO) and increases intracellular cGMP, thereby relaxing vascular smooth muscles. Consequently, cardiac preload and afterload are lessened, which leads to improved hemodynamics in congestive cardiac failure. Collateral blood flow pathways are also dilated as well as relatively thick coronary arteries; therefore, coronary blood flow increases. Isosorbide dinitrate is a vasodilator selective for veins but decreases blood pressure. The time to the effect of isosorbide nitrate is longer than that of nitroglycerine, while the duration of its effect is longer than that of nitroglycerine.[3]

PHYSICOCHEMISTRY

Structural formula:



Manufacturer and Distributor
TOWA PHARMACEUTICAL CO., LTD.
2-11, Shinbashi-cho, Kadoma, Osaka 571-8580
Japan

Nonproprietary name:
Isosorbide Dinitrate
Chemical name:
1,4:3,6-Dianhydro-D-glucitol dinitrate
Molecular formula:
$C_6H_8N_2O_8$
Molecular weight:
236.14
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

Stability test

A long-term storage study using final packaging products (at room temperature for 3 years) has proved that Isosorbide Dinitrate SR Tablets 20mg "TOWA" is stable for 3 years under normal distribution conditions in the market [4]..

PACKAGING

ISOSORBIDE DINITRATE SR TABLETS 20mg "TOWA":
Boxes of 100 tablets, 1,000 tablets (PTP),
Polyethylene containers of 1,000 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
3) The 16th revision Japanese Pharmacopoeia explanatory, C-2057, 2011
4) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test