

Revised: July 2009 (11th version)

Standard Commodity Classification No. of Japan
872149

- Once a day α_1 blocking antihypertensive agent -**Detantol[®] R Tablets 3mg****Detantol[®] R Tablets 6mg**

<Bunazosin Hydrochloride sustained-release formulation>

Prescription drug

Storage
DETANTOL R should be stored at room temperature. DETANTOL R should be protected from light and moisture after opening package.

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

	Tablets 3 mg	Tablets 6 mg
Approval No.	20700AMZ00013000	20700AMZ00014000
Date of listing in the NHI reimbursement price	Mar 1995	Mar 1995
Date of initial marketing in Japan	May 1995	May 1995
Date of latest reexamination	Dec 2001	
International birthdate	Apr 1985	

Caution : Use only as directed by a physician.

CONTRAINDICATIONS (DETANTOL R is contraindicated in the following patients.)

Patients with a history of hypersensitivity to any ingredients of DETANTOL R.

DESCRIPTION**1. Composition****Tablets 3 mg:**

Each white, film-coated, sustained-release tablet contains 3 mg of bunazosin hydrochloride.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, titanium oxide, sucrose esters of fatty acids, calcium stearate, purified shellac, talc, medium chain fatty acid triglyceride, lactose hydrate, hydroxypropylcellulose, hypromellose and macrogol 6000 as inactive ingredients.

Tablets 6 mg:

Each white, film-coated, sustained-release tablet contains 6 mg of bunazosin hydrochloride.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, titanium oxide, sucrose esters of fatty acids, calcium stearate, purified shellac, talc, medium chain fatty acid triglyceride, lactose hydrate, hydroxypropylcellulose, hypromellose and macrogol 6000 as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
DETANTOL R Tablets 3 mg	Film-coated tablets				White
	E 41	Diameter (mm) 5.6	Weight (mg) 83	Thickness (mm) 3.1	
DETANTOL R Tablets 6 mg	Film-coated tablets				White
	E 43	Diameter (mm) 7.2	Weight (mg) 166	Thickness (mm) 3.9	

INDICATIONS

Hypertension

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 3 to 9 mg of bunazosin hydrochloride once daily. The administration should be started at a dose of 3 mg once daily and the maximum daily dose of 9 mg should not be exceeded.

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

- (1) Patients with hepatic function disorders
[Since DETANTOL R is conjugated in the liver and excreted in feces, the blood bunazosin concentration may increase in patients with hepatic function disorders.]
- (2) Patients with renal function disorders
[The peak blood bunazosin concentration may increase in patients with renal function disorders. See "Pharmacokinetics" section.]
- (3) Elderly patients
[See "Use in the Elderly" section.]

- (4) Patients under treatment with phosphodiesterase type 5 inhibitors
[See “Drug Interactions” section.]

2. Important Precautions

- (1) Dizziness on standing up, dizziness or other symptoms due to orthostatic hypotension may occur during the early course of treatment or after a sharp increase in dosage. Patients should be warned against working at heights, engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.
- (2) Since orthostatic hypotension may occur, blood pressure should be measured not only in the supine position but also in the standing or sitting position. Blood pressure should be controlled in the sitting position in consideration of blood pressure variation after a postural change.
- (3) Dizziness on standing up, dizziness, nausea, chest discomfort, dyspnea or other symptoms may occur during the early course of treatment or after a sharp increase in dosage. In the event of such symptoms, appropriate treatment, such as placing the patient in the supine position, should be taken. Symptomatic treatment, such as administration of a vasopressor, should be initiated, if necessary, paying attention to any complications the patient may have and the patient's medical history.

3. Drug Interactions

Precautions for coadministration (DETANTOL R should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Diuretics Other antihypertensive agents	The effects of DETANTOL R may be enhanced. Caution should be exercised and appropriate measures should be taken, such as reducing in dosage.	Due to potentiation of additive effect of the antihypertensive action.
Rifampicin	The effects of DETANTOL R may be decreased.	The blood bunazosin hydrochloride concentration may be decreased due to induction of hepatic drug metabolizing enzymes by rifampicin.
Phosphodiesterase type 5 inhibitors Vardenafil hydrochloride hydrate Sildenafil citrate, etc.	There have been reports of symptoms occurring together with a lowering of blood pressure when they were administered concomitantly with an α -blocker.	Phosphodiesterase type 5 inhibitors have a vasodilatory mechanism, and may therefore enhance the hypotensive effect of bunazosin hydrochloride.

4. Adverse Reactions

Adverse reactions were reported in 223 of 3,817 patients. (5.84%) (At the end of the reexamination period)

(1) Clinically significant adverse reactions

Syncope and unconsciousness:

Syncope (5% > $\geq 0.1\%$) and unconsciousness (<0.1%) (mostly due to temporary hypotension) may occur. In the event of such symptoms, discontinuation of the medication and appropriate measures, such as placing the patient in the supine position, should be taken.

(2) Other adverse reactions

	5% > $\geq 0.1\%$	<0.1%	Incidence unknown
Psychoneurologic	Dizziness, headache, insomnia, malaise, sleepiness, tinnitus and dull headache	Numbness, decreased consciousness and weakness	
Cardiovascular	Dizziness on standing up, palpitations, tachycardia and hypotension	A sensation of chest pressure, chest discomfort and postural hypotension	
Gastrointestinal	Nausea	Vomiting, anorexia, stomach discomfort, diarrhea, thirst and constipation	Abdominal pain
Hepatic		Elevation of AST(GOT), ALT(GPT) and γ -GTP, etc.	
Urinary	Pollakiuria	Urinary incontinence and nocturia	
Hypersensitivity <small>(note)</small>	Rash	pruritus	
Others	Facial hot flushes, edema and feeling of hot flushes	Shoulder stiffness, diaphoresis and blurred vision	Nasal obstruction and respiratory distress

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

5. Use in the Elderly

When DETANTOL R is to be used in elderly patients, careful administration, paying attention to the following points, is required. The initial dosage should be low (3 mg/day), and the patient's condition observed after administration.

- (1) In the elderly, an excessive reduction in blood pressure is generally considered to be unfavorable [Cerebral infarction may occur].
- (2) Adverse reactions are likely to occur in elderly patients, partly because most of them have impaired hepatic and renal functions and partly because many of them tend to weigh less than normal. [For information about patients with renal function disorders, see paragraph 3. of “Pharmacokinetics” section.]
- (3) Elderly patients should be carefully observed during the treatment and caution should be exercised when the dose is increased. If an excessive reduction in blood pressure results from the use of DETANTOL R, the dosage should be reduced or treatment discontinued. Alternatively, consideration should be given to switching the patient to a different type of antihypertensive drug. [See “Important Precautions” section.]

6. Use during Pregnancy, Delivery or Lactation

- (1) DETANTOL R should only be used in pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment.
[DETANTOL R has been reported to have a teratogenic effect in an animal study (in rats).]

- (2) If DETANTOL R is administered to nursing mothers, it is advisable to discontinue breast feeding during treatment.

[DETANTOL R has been reported to be excreted in breast milk in an animal study (in rats).]

7. Pediatric Use

The safety in children has not been established (no clinical experience).

8. Precautions concerning Use

(1) Oral administration

The patient should be instructed not to bite or chew the tablets, but to swallow them. If the tablet is crushed, the blood bunazosin concentration may show a temporary rise, increasing the likelihood of adverse reactions.

(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) For an analog compound (prazosin hydrochloride), it has been reported that acute febrile polyarthritis occurred in one hypertensive patient who had renal arteriosclerosis, other arteriosclerosis and vascular disorders, such as aneurysms in the legs and other sites.
- (2) Intraoperative floppy iris syndrome has been reported in patients currently taking or having a history of treatment with α_1 -blockers. This syndrome is considered to be caused by their α_1 -blocking action.

PHARMACOKINETICS

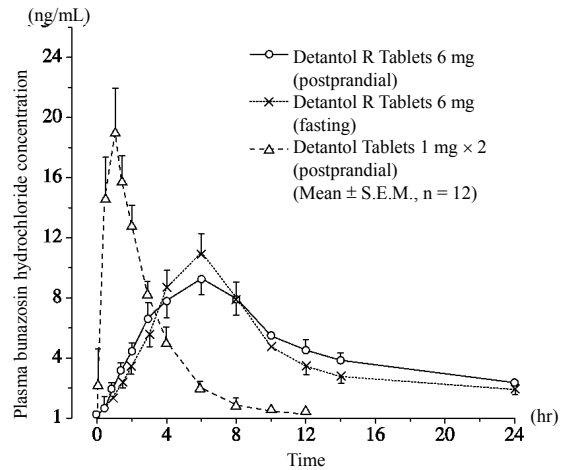
1. Blood concentration

(1) Bioavailability in healthy adult volunteers

DETANTOL or DETANTOL R was administered orally to 12 healthy adult male volunteers at a dose of 2 mg (two 1 mg tablets) or 6 mg (one 6 mg tablet), respectively, and the plasma bunazosin concentrations were compared between the two groups. The relative bioavailability of DETANTOL R was determined to be 81.1% and DETANTOL R showed prolonged bioavailability as determined from the mean residence time (MRT).¹⁾

(2) Effect of meal

When one DETANTOL R 6 mg Tablets was administered to each of 12 healthy adult male volunteers during fasting or after a meal, the meal was seen to have no effect on the absorption of DETANTOL R.¹⁾



Time course of mean plasma concentration after single oral administration of bunazosin hydrochloride

Pharmacokinetic parameters after single oral administration of bunazosin hydrochloride

Administration condition	C _{max} (ng/mL)	t _{max} (hr)	AUC (ng · hr/mL)	R.B.A. (%)	MRT (hr)
DETANTOL R 6 mg (postprandial)	10.19 ± 1.10	5.25 ± 0.54	132.73 ± 15.42 ²⁾	81.07 ± 5.98	13.02 ± 0.66
DETANTOL R 6 mg (fasting)	11.38 ± 1.32	6.00 ± 0.35	123.03 ± 16.50 ²⁾	74.05 ± 5.24	12.77 ± 0.66
DETANTOL 2 mg (postprandial)	22.48 ± 2.41	0.96 ± 0.16	54.68 ± 5.72 ¹⁾	100.00 ± 0.00	2.60 ± 0.15

R.B.A.: Relative bioavailability

Mean ± S.E.M., n=12

MRT: Mean residence time

1) AUC (0-∞) 2) AUC (0-48hr)

2. Bioequivalence

When either DETANTOL R Tablets 3 mg or 6 mg were administered to 24 healthy adult volunteers at a dose of 6 mg of bunazosine hydrochloride, the changes in the plasma bunazosine concentration for the two dosage forms were shown to be equivalent.

3. Pharmacokinetics in hypertensive patients with impaired renal function

DETANTOL R was administered orally to 5 hypertensive patients with impaired renal functions [IRF] or 6 hypertensive patients with normal renal functions [NRF] at a dose of 6 mg for 8 consecutive days. The peak plasma bunazosin concentrations were higher in hypertensive patients in the IRF group than in the patients in the NRF group on days 1 and 8.²⁾

Pharmacokinetic parameters after single- and repeated-dose administration of DETANTOL R in the NRF and IRF group

	C _{max} (ng/mL)		t _{max} (hr)		AUC ₀₋₂₄ (ng · hr/mL)	
	NRF group	IRF group	NRF group	IRF group	NRF group	IRF group
Single-dose administration	10.1 ± 2.0	15.9 ± 1.2	3.7 ± 0.3	4.4 ± 1.0	115.5 ± 20.2	184.1 ± 25.4
Repeated-dose administration	10.7 ± 2.3	19.5 ± 1.9	6.0 ± 1.4	4.0 ± 1.1	138.4 ± 32.4	246.4 ± 49.0

Mean ± S.E.M., n=5-6

Single- and repeated-dose ... Paired *t*-test

NRF group and IRF group ... Student's *t*-test

CLINICAL STUDIES

Clinical trials, including a double-blind comparative clinical trial, have been carried out in a total of 466 patients. The results of these trials may be summarized as follows (patients judged to be "unassessable" were excluded from the evaluation of antihypertensive effect (remarkably to moderately decreased in blood pressure.)³⁻⁷⁾

1. Mild or moderate essential hypertension

The antihypertensive effect in patients with mild to moderate essential hypertension was 63.2% (225/356). In comparative trials with DETANTOL R alone and in combination with other drugs, the antihypertensive effect was 49.4% (38/77) with DETANTOL R alone, 73.7% (28/38) with DETANTOL R and a diuretic, and 57.9% (11/19) with DETANTOL R and a β -blocker. A stable antihypertensive effect was obtained during long-term administration over 6 months or longer. In a double-blind clinical trial with DETANTOL R (3 to 9 mg s.i.d.) and DETANTOL (1.5 to 6 mg t.i.d.), the antihypertensive effect and usefulness were comparable for the two dosage forms.³⁻⁵⁾

2. Severe hypertension

The antihypertensive effect in patients with severe hypertension was 80.6% (25/31).⁶⁾

3. Hypertension accompanied by renal function disorders

The antihypertensive effect in hypertensive patients with renal function disorders was 69.2% (18/26).⁷⁾

PHARMACOLOGY

1. Selective blocking of cardiovascular α_1 -receptors

(1) In *in vitro* experiments on rat seminal ducts, bunazosin hydrochloride selectively blocks α_1 -receptors without affecting α_2 -receptors. It does not affect the negative feedback mechanism of noradrenaline release through α_2 -receptors in the sympathetic nerve endings, hence noradrenaline is not released in excess after the administration of bunazosin hydrochloride.⁸⁾

(2) In *in vitro* experiments on guinea pig pulmonary arteries and mesenteric veins, bunazosin hydrochloride selectively blocks α_1 -receptors and does not cause α_2 -blockade even at high concentrations.⁹⁾

2. Antihypertensive action through decrease in peripheral vascular resistance

Bunazosin hydrochloride exhibits a hypotensive action in spontaneously hypertensive rats (SHR), rats with DOCA and salt-induced hypertension, and dogs with renal hypertension. This antihypertensive action of bunazosin hydrochloride is due to vasodilation resulting from selective blockade of peripheral vessel α_1 -receptor. Further, bunazosin hydrochloride does not cause an increase in humoral pressor factors, a response associated with hypotension.¹⁰⁻¹²⁾

PHYSICOCHEMISTRY

Nonproprietary name: Bunazosin Hydrochloride (JAN)

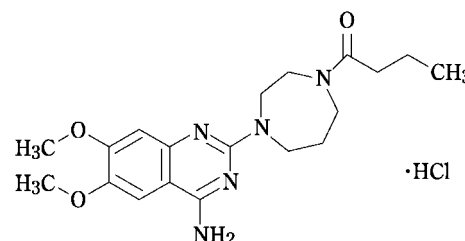
Chemical name:

4-Amino-2-(4-butanoyl-1,4-diazepan-1-yl)-6,7-dimethoxyquinazoline monohydrochloride

Molecular formula: C₁₉H₂₇N₅O₃ · HCl

Molecular weight: 409.91

Structural formula:



Description:

Bunazosin hydrochloride occurs as a white, crystalline powder. It is very soluble in formic acid, slightly soluble in water and in methanol, very slightly soluble in ethanol (99.5), and practically insoluble in diethyl ether.

Melting point: about 273°C (with decomposition)

Partition coefficient: 0.215 (water : 1-octanol)

PACKAGING

DETANTOL R Tablets 3 mg:

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

DETANTOL R Tablets 6 mg:

Boxes of 100, 140 (14 Tabs.×10) and 500 in press-through packages.

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REQUEST FOR LITERATURE SHOULD BE MADE TO:

Safety Management Department

Fax: 03-3811-2710

Eisai Co., Ltd.

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Customer Information Service

Free Dial: 0120-419-497

Eisai Co., Ltd.

Manufactured and marketed by:

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6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088

BRAND NAMES IN OTHER COUNTRIES

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