

Harnal® Capsule

COMPOSITION

Harnal Capsule 0.2 mg is hard capsule containing 0.2 mg of tamsulosin hydrochloride.

PHARMACOLOGY

1) Pharmacological Effects

a) Effects in humans

In a receptor binding assay using human prostate preparations, tamsulosin hydrochloride was 2.2 times more potent than

prazosin hydrochloride and 40 times more so than phentolamine mesylate in α_1 -receptor blocking activity.

b) Effects in animals

(1) Blockade of α -adrenergic receptors

In a receptor binding assay using isolated rat cerebral membrane and an in vitro experiment using isolated rabbit aorta,

tamsulosin hydrochloride inhibited α_1 -receptors selectively and competitively. Its action was 1/2.2 to 22 times more

potent than prazosin hydrochloride and 45 to 140 times more potent than phentolamine mesylate.

In vitro experiments using isolated rabbit aorta, isolated rat vas deferens and isolated guinea pig intestine, tamsulosin

hydrochloride proved to be 5,400 to 24,000 times more selective for α_1 -receptors than for α_2 -receptors.

(2) Effect on the lower urinary tract (urethra and urinary bladder) and prostate

In a receptor binding assay using isolated smooth muscle from the rabbit urethra, prostate and urinary bladder base,

tamsulosin hydrochloride was times more potent than prazosin hydrochloride in α_1 -receptor blocking activity,

and 87 to 320 times more potent than phentolamine mesylate. In anesthetized dogs, the drug inhibited the α_1 -agonist

(phenylephrine)-induced increase in intraurethral pressure with 13 times greater potency than the increase in diastolic

blood pressure.

(3) Improvement of bladder outlet obstruction

In anesthetized male dogs, tamsulosin hydrochloride decreased urethral pressure in the prostatic zone of the intraurethral

pressure curve. In anesthetized rats, however, the drug did not affect bladder contraction or threshold intravesical

pressure.

2) Mechanism of action

Tamsulosin hydrochloride decreases urethral pressure in the prostatic zone of the intraurethral pressure curve by inhibiting α_1 -receptors in the urethra and prostate, thus improving bladder outlet obstruction associated with benign prostatic hyperplasia.

PHARMACOKINETICS

1) Plasma concentration

Plasma concentration of unchanged drug reached a peak at 7 to 8 h after a single oral administration of 0.1 to 0.6 mg tamsulosin hydrochloride to healthy male adults. The half-life was 9.0 to 11.6 h. C_{\max} and AUC increased nearly in a dose-dependent manner. In a 7-day repeated oral administration study, the half life was slightly prolonged and plasma concentration reached a steady state on day 4.

Dosage (mg)	T_{\max} (h)	C_{\max} (ng/ml)	$T_{1/2}$ (h)
0.1	7.0	3.2	11.6
0.2	8.0	5.7	9.0
0.4	7.0	15.6	10.8
0.6	7.5	15.6	9.8

Tamsulosin hydrochloride at a dose of 0.2 mg was orally administered to 11 patients with renal dysfunction. Their blood pressure did not decrease, but an increase in plasma concentration of unchanged drug was observed in 2 patients with serious renal impairment. The plasma concentrations of the drug were intimately correlated with an increase in plasma concentration of $\alpha 1$ -AGP ($\alpha 1$ -acid glycoprotein). This increase in plasma concentration of the drug may be caused by binding of the tamsulosin hydrochloride to plasma $\alpha 1$ -AGP. However, the plasma concentration of the unbound drug, which is presumed to be directly related with the appearance of the drug effects and adverse reactions, were almost the same in these patients as well as in persons with normal renal function regardless of the plasma concentration of $\alpha 1$ -AGP

2) Metabolism and excretion

Single doses of tamsulosin hydrochloride at 0.1 to 0.6 mg were orally administered to healthy male adults. The excretion rate of the unchanged drug in the urine up to 30 h after administration remained almost constant at 12 to 14%. No significant changes in the excretion rate after repeated administration were observed.

INDICATIONS

Bladder outlet disturbance associated with benign prostatic hyperplasia.

PRECAUTION

1) Careful Administration (This product should be administered with caution in the following patients.)

- Patients with orthostatic hypotension [Symptoms may be exacerbated]
- Patients with hepatic dysfunctions [Plasma drug concentration may be increased]
- Patients with mild to moderate renal dysfunction [An increase in plasma drug concentrations may result]
- The elderly patients

2) Important Precautions

- Use with caution concerning dosage and administration. Overdosage may cause a decrease in blood pressure.
- Blood pressure in the orthostatic position may decrease. Patients must be watched for any changes in blood pressure

occurring with postural change.

- c) The drug does not eliminate the cause of the disease, but gives symptomatic relief. If the expected response does not result, surgical therapy or other alternative procedures should be considered.
- d) Since the drug may produce dizziness, patients should be cautioned about driving, operating machinery or performing hazardous tasks.
- e) Before the start treatment, patients should be asked whether they are taking any antihypertensive drugs. If any such drugs are used, blood pressure during treatment should be monitored closely. If a decrease in blood pressure is observed, the dose should be reduced, the treatment discontinued or other appropriate measures taken.

3) Cautions in use

Patients should be instructed not to chew the granules contained within.

4) Use in patients with micturition syncope is not advised

CONTRAINDICATIONS

(This product is contraindicated in the following patients.)

- 1) Patients with a history of hypersensitive reactions to this drug
- 2) Patients who take vardenafil HCl hydrate (See "Drug Interactions")
- 3) Severe hepatic insufficiency
- 4) Severe impaired renal function (An excessive increase in plasma drug concentration may be induced in patients with impaired renal function, but complete pharmacokinetic data in such patients are not yet available. Therefore, patients with severe impaired renal function should not use this drug.)

ADVERSE REACTIONS

1) Clinically significant adverse reactions

a) Syncope unconsciousness (Incidence unknown): As transient unconsciousnesses or etc. may appear with the decrease

of blood pressure, the patient should be observed carefully. If such reactions are observed during treatment, discontinue treatment and institute appropriate medical therapy.

b) Hepatic dysfunction or jaundice (Incidence unknown): As increases of AST (GOT), ALT (GPT), or jaundice may

appear, the patient should be observed carefully. If such reactions are observed during treatment, appropriate measures such as drug discontinuation should be taken.

2) Other adverse reactions

	5 % > ≥0.1%	<0.1%	Incidence unknown
Nervous system/ Psychiatric	Dizziness Giddiness	Dizziness on standing up, headache, sleepiness	Nervousness

Cardiovascular		Blood pressure drooped, orthostatic hypotension, tachycardia, palpitation	Arrhythmia
Hypersensitivity notes)		Itching, rash	Urticaria
Gastrointestinal	Stomach discomfort	Nausea/vomiting, dypsosis, obstipation, stomach heaviness, stomachache, appetite decreased, diarrhea, dysphagia	
Others		Nasal obstruction, edema, urinary incontinence, burning sensation of pharynx, generalized fatigue	Dysgeusia, gynaecomastia, priapism

Note) If such a reaction develops, discontinue treatment.

DRUG INTERACTIONS

[Contraindications for coadministration]

(This product should not be coadministered with the following drug)

Drugs	Sign, Symptoms, and Treatment	Mechanism and Risk Factors
Vardenafil HCl hydrate	It has been reported that concomitant use of vardenafil HCl hydrate and Harnal Capsules may cause hypotension or orthostatic hypotension	Since Harnal Capsules exhibit an α -blocking activity the vasodilatory hypotensive action of vardenafil HCl hydrate may be enhanced by concomitant use.

[Precautions for coadministration]

(This product should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Anti hypertensive	Take with Precautions by decreasing doses as orthostatic hypotension may occur	Patient who take antihypertensives may experience a decrease in blood pressure when they stand.
Sildenafil citrate	It has been reported that concomitant use of sildenafil citrate and other α -blockers may cause hypotension accompanied by subjective symptoms such as dizziness	Since Harnal Capsules exhibit an α -blocking activity, the vasodilatory hypotensive action of sildenafil citrate may be enhanced by concomitant use.

OVERDOSE

No cases of acute overdose have been reported. However, acute hypotension is likely to occur after overdosage in which case cardiovascular..... support should be given. Blood pressure can be restored and the heart rate brought back to normal by lying the patient down. If this does not help then volume expanders, when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied. Dialysis is unlikely to be help as tamsulosin is very highly bound to plasma protein. Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate can be administrative.

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 0.2mg-0.4mg of tamsulosin hydrochloride once daily after meals. The dosage may be adjusted depending on the patient's age and symptoms.

USE IN ELDERLY

Elderly patients often have renal hypofunction. This product should be administered to such patients with caution and careful monitoring. If efficacy is not noted at 0.2 mg, the dose should not be further increased, and other appropriate measures must be taken.

STORAGE

Store in tight container, at room temperature (25^o-30^oC)

PACKAGING

HARNAL 0.2mg Capsule-Boxes of 3 strips @ 10 Capsules.
Reg. No. DKI9779400401A2

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by: Astellas Pharma Inc., Tokyo, Japan.

Imported by: PT Astellas Pharma Indonesia, Jakarta, Indonesia

Packed by:

PT. Combiphar
Bandung, Indonesia