-Reliever of bladder outlet obstruction associated with benign prostatic hyperplasia-

**Harnalidge® D Tablets 0.2 mg**

(Tamsulosin HCl)

**Storage:** Store in a tight container at room temperature (15~30℃)
**Expiration date:** See the expiration date on the package, etc
**License number:** 024403
**Use only pursuant to the prescription of a physician**

<table>
<thead>
<tr>
<th>&lt;Composition · Description&gt;</th>
<th>Brand Name</th>
<th>Active ingredient (in each tablet)</th>
<th>Appearance (mm)</th>
<th>Weight (g)</th>
<th>Color</th>
<th>Identification code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harnalidge® D Tablets 20 mg</td>
<td>Tamsulosin HCl 0.2 mg</td>
<td>Orally disintegrating tablet Diameter: 8.5 mm Thickness: 4.2 mm</td>
<td>0.2</td>
<td>White</td>
<td>557</td>
<td></td>
</tr>
</tbody>
</table>

Excipients: Microcrystalline cellulose spheres, Hydropropylmethylcellulose, Ethylcellulose, Methacrylic acid copolymer LD, Sodium lauryl sulfate, Polysorbate 80, Cetanol, Ethyl acrylate-methyl methacrylate copolymer, Polyoxyethylene nonylphenyl ether, D-Mannitol, Lactose, Maltose syrup powder, Calcium stearate.

**<Indication>**

Bladder outlet obstruction associated with benign prostatic hyperplasia.

**<Dosage and Administration>**

The recommended adult should be given an initial dose of tamsulosin hydrochloride 0.2 mg. Oral use, one tablet daily. If efficacy is not sufficient at 0.2 mg, the dosage can be adjusted to 0.4 mg. The maximum daily dosage is 0.4 mg.

Use in the elderly

Elderly patients are more likely to experience renal dysfunction. Such patients should be given an initial daily dose of 0.1 mg, and the dose can be increased to 0.2 mg after carefully monitored. If efficacy is not noted at 0.2 mg, the dose should not be increased further, and other appropriate pleasures must be taken.

**<Precautions>**

1. **Contraindications**

   - Hypersensitivity to tamsulosin hydrochloride or any of the excipients.
   - A history of orthostatic hypotension.
   - Severe hepatic insufficiency.

2. **Important precautions**

   (1) As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin, as a result of which syncope can occur (rarely). At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. When start using tamsulosin, the patient should be advised to avoid the possibility of injury resulted from syncope.
(2) When using the maximum daily dosage (0.4 mg), patients should be advised to avoid the possibility of injury resulted from syncope.

(3) The treatment of patients with severe renal impairment (creatinine clearance of < 10 mL/min) should be approached with caution, as these patients have not been studied.

(4) The ‘Intraoperative Floppy Iris Syndrome’ (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with tamsulosin in patients for whom cataract surgery is scheduled is not recommended. Discontinuing tamsulosin 1-2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping of therapy prior to cataract surgery has not yet been established.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

(5) Tamsulosin is mainly metabolized by CYP3A4 and CYP2D6, Harnalidge® D Tablets 0.2 mg 0.4 mg should not be given in combination with strong inhibitors of CYP3A4 (ex. Ketoconazole). Tamsulosin should be used with caution in combination with moderate inhibitors (ex. erythromycin) of CYP3A4 or in combination with strong inhibitors (ex. paroxetine) or moderate inhibitors (ex. terbinafine) of CYP2D6, especially in patients with poor metaboliser.

(6) Tamsulosin hydrochloride should be used with caution in combination with cimetidine.

(7) Tamsulosin hydrochloride should not be used in combination with other α-adrenoceptor antagonists.

(8) Caution is advised when α-adrenoceptor antagonists including tamsulosin hydrochloride are co-administered with PDE5 inhibitors. α-Adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

(9) Caution should exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

(10) The tablets disintegrate in the mouth, but are not absorbed through the oral mucosa. Therefore, the patients should be instructed to swallow the dissolved tablet with saliva or a drink of water.

(11) This product does not eliminate the cause of the disease, but gives symptomatic relief. If the expected response does not result, surgical therapy or other alternative procedure should be considered.

(12) Since this product may induce symptoms such as dizziness, patients should be cautioned against performing hazardous activities, such as working at altitudes or driving a car.

(13) Before the start of 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. Drug interaction

(1) Interaction studies have only been performed in adults.

(2) No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril or theophylline.
(3) Concurrent use with cimetidine brings about a rise in plasma levels of tamsulosin, and should be carefully administered concomitantly, whereas with furosemide brings a fall, but as levels remain within the normal range posology need not be adjusted.

(4) In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide and chlormadinone. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

(5) Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin hydrochloride. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and Cmax of tamsulosin hydrochloride by a factor of 2.8 and 2.2, respectively. The effects of concomitant administration of moderate CYP3A4 inhibitors (ex. erythromycin) on the pharmacokinetics of tamsulosin hydrochloride have not been evaluated.

(6) Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a Cmax and AUC of tamsulosin that had increased by a factor of 1.3 and 1.6, respectively.

(7) A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when tamsulosin hydrochloride 0.4mg is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin hydrochloride 0.4mg should not be used in combination with strong inhibitors of CYP3A4 (ex. ketoconazole).

(8) The effects of concomitant administration of a moderate CYP2D6 inhibitor (ex. terbinafine) on the pharmacokinetics of tamsulosin hydrochloride have not been evaluated.

(9) Concurrent administration of other α₁-adrenoceptor antagonist or PDE-5 inhibitor (ex. sildenafil) could lead to hypotensive effects.

(10) Precautions for coadministration.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, symptoms, and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td>Take precautions by decreasing doses as orthostatic hypotension may occur.</td>
<td>Autoregulation of blood pressure may be impaired in patients taking antihypertensives.</td>
</tr>
<tr>
<td>Phosphodiseterase-5 inhibitor</td>
<td>It has been reported that concomitant use of Phosphodiseterase-5 inhibitors and this product may cause hypotension.</td>
<td>Since this product exhibits an α-blocking activity, the vasodilatory hypotensive action of Phosphodiseterase-5 inhibitors may be enhanced by concomitant use.</td>
</tr>
</tbody>
</table>

4. Adverse reactions

Adverse reactions (including abnormalities in clinical laboratory findings) to this product were observed in 104 (2.2%) of 4,724 patients investigated in the clinical trials until approval, and in drug-use results surveys. The major adverse reactions were dizziness and stomach discomfort.

(At the end of latest reexamination: November 2003)
(1) Clinically significant adverse reactions

1) Syncope/unconsciousness (Incidence unknown):
Since transient unconsciousness etc. may appear with a decrease in blood pressure, patients should be carefully observed. If any abnormal finding are observed during treatment, administration should be discontinued and appropriate should be taken.

2) Hepatic function disorder or jaundice (Incidence unknown):
Since increases of AST(GOT), ALT(GPT), or jaundice may appear, patients should be carefully observe. If any abnormal findings are observed during treatment, appropriate measures such as drug discontinuation should be taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>5%&gt;, ≥0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psyconeurologic</td>
<td>Dizziness, Swaying feeling</td>
<td>Dizziness on standing up, Headache, Sleepiness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Blood pressure decreased, Orthostatic hypotension (&gt;1/1000, &lt;1/100), Tachycardia, Palpitations.</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Hypersensitivity (note)</td>
<td>Itching, Rash</td>
<td>Urticaria, Erythema multiforme</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Stomach discomfort</td>
<td>Queasy, Vomiting, Thirst, Constipation, Stomach heaviness, Gastralgia, Anorexia, Diarrhoea, Dysphagia</td>
</tr>
<tr>
<td>Others</td>
<td>Ejaculation disorder (&gt;1/100, &lt;1/10)</td>
<td>Nasal congestion, Oedema, Urinary incontinence, Burning sensation of pharynx, General malaise</td>
</tr>
</tbody>
</table>

Note) Discontinue treatment.

5. Precautions concerning use

(1) Caution in dispensing:
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to taking this product. (It has been reports that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complication such as mediastinitis.)

(2) Caution in oral administration:
2) The tablets can be soaked in saliva on the tongue, lightly mashed between the tongue and hard palate, and then swallowed with saliva alone.
3) The tablets should not be taken without water if the patients is lying down.
1. Plasma concentration

When a single dose of Harnalidge D tablets 0.2 mg or Harnalidge 0.2 mg capsules is orally administrated to healthy male adults using a cross-over method, the plasma concentration of unchanged tamsulosin hydrochloride is shown below.\(^1\)

<table>
<thead>
<tr>
<th>Drug product</th>
<th>Dosage (mg)</th>
<th>(C_{\text{max}}) (ng/mL)</th>
<th>AUC(_t) (ng \cdot h/mL)</th>
<th>(T_{1/2}) (h)</th>
<th>(T_{\text{max}}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harnalidge D tablets 0.2 mg</td>
<td>0.2 mg</td>
<td>4.34±1.32</td>
<td>63.5±22.9</td>
<td>11.70±2.96</td>
<td>7.00±2.04</td>
</tr>
<tr>
<td>Harnalidge 0.2 mg capsules</td>
<td>0.2 mg</td>
<td>4.71±1.81</td>
<td>62.0±20.8</td>
<td>10.27±3.27</td>
<td>7.83±2.42</td>
</tr>
</tbody>
</table>

The plasma concentration of the unchanged reached its peak 7 to 8 h after a single oral administration of 0.1 to 0.6 Harnalidge capsules to healthy male adults. The half-life was 9.0 to 11.6 h\(^3\). The \(C_{\text{max}}\) and AUC increased in a nearly dose-dependent manner. In a 7-day repeated oral administration study, the half-life was slightly prolonged and plasma concentrations reached a steady state on day 4\(^3\).

"<Pharmacokinetic parameters for Harnalidge capsules for clinical dosing>"

<table>
<thead>
<tr>
<th>Dosage (mg)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(C_{\text{max}}) (ng/mL)</th>
<th>(T_{1/2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>7.0</td>
<td>3.2</td>
<td>11.6</td>
</tr>
<tr>
<td>0.2</td>
<td>8.0</td>
<td>5.7</td>
<td>9.0</td>
</tr>
<tr>
<td>0.4</td>
<td>7.0</td>
<td>15.6</td>
<td>10.8</td>
</tr>
<tr>
<td>0.6</td>
<td>7.5</td>
<td>15.6</td>
<td>9.8</td>
</tr>
</tbody>
</table>

(Note) The approved daily dose for this product is 0.4 mg.

Harnalidge 0.2 mg capsules were orally administered to 11 patients with renal dysfunction. Their blood pressure did not decrease, but an increase in the plasma concentration of tamsulosin hydrochloride was observed in 2 patients with serious renal impairment. The plasma concentrations of the drug were intimately correlated with an increase in the plasma concentration of \(\alpha_1\)-AGP (\(\alpha_1\)-acid glycoprotein). This increase in the plasma concentration of the drug may be caused by the 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 to the appearance of the effects and adverse reactions of tamsulosin hydrochloride, was almost the same for
these patients as for persons with normal renal function, regardless of the plasma concentration of $\alpha_1$-AGP\(^4\).

2. Metabolism and excretion

(1) Single doses of HARNAL Capsules of 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%\(^2\). No significant changes in the excretion rate after repeated administrations were observed\(^3\).

(2) Tamsulosin has a low first pass effect, being metabolized slowly. Most tamsulosin is present in plasma in the form of unchanged active substance. It is mainly metabolized in the liver.

(3) In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.

(4) In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin hydrochloride metabolism by other CYP isozymes. Inhibition of CYP3A4 and CYP2D6 drug metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride (see “2. Important precautions” and “3. Drug interaction” of “Precautions”). The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

(5) None of the metabolites are more active than the original compound.

(6) The approved daily dose for this product is 0.4 mg.

3. Bioequivalence

When Harnalidge D tablets or Harnalidge capsules were orally administered to humans, the plasma concentration-time profile of the unchanged drug was almost equivalent between the two formulations, demonstrating their bioequivalence\(^1\)\(^5\)\(^6\).

**<Clinical Studies>**

This product significantly decreased intraurethral pressure in the prostatic urethra\(^7\), and improved urinary flow rate and residual urine volume in a dose-dependent manner\(^8\)\(^9\). The evaluation results of overall improvement in 276 cases are presented in the following table. Results of a double-blind comparative study showed that Harnalidge capsules administered in a 0.2 mg once daily dose was clinically useful in easing symptoms of benign prostatic hyperplasia\(^10\).

<table>
<thead>
<tr>
<th>Administration method</th>
<th>Ratio of moderate or better improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mg once daily</td>
<td>28.3% (15/53)</td>
</tr>
<tr>
<td>0.2 mg once daily</td>
<td>37.3% (62/166)</td>
</tr>
<tr>
<td>0.4 mg once daily</td>
<td>38.6% (22/57)</td>
</tr>
</tbody>
</table>

(Note) The approved daily dosage for this product is 0.4 mg.

**<Pharmacology>**

1. Pharmacological effects

(1) Effects in humans

In a receptor binding assay using human prostate preparations, this product was 2.2 times more potent than prazosin hydrochloride and 40 times more so than phentolamine mesylate in $\alpha_1$-receptor blocking activity\(^11\).
(2) Effects in animals

1) Blockade of $\alpha$-adrenergic receptors$^{(12)(13)}$

In a receptor binding assay using isolated rat cerebral membrane and in vitro experiment using isolated rabbit aorta, this product inhibited $\alpha_1$-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 $\alpha_1$-receptors than for $\alpha_2$-receptors.

2) Effect on the lower urinary tract (urethra and urinary bladder) and prostate$^{(14)-(16)}$

In a receptor binding assay using isolated smooth muscle from rabbit urethra, postate and urinary bladder base, tamsulosin hydrochloride was 23 to 98 times more potent than prazosin hydrochloride in $\alpha_1$-receptor blocking activity, and 87 to 320 times more potent than phentolamine mesylate. In anesthetized dogs, the drug inhibited the $\alpha_1$-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$^{(17)}$

In anesthetized male dogs, this product decreased urethral pressure in the prostatic zone of the intraurethral pressure curve. In anesthetized rats, however, the drug did not affect rhythmic bladder contraction or threshold intravesical pressure.

2. Mechanism of action

This product decreases urethral pressure in the prostatic zone of the intraurethral pressure curve by inhibiting $\alpha_1$-receptors in the urethra and prostate, thus improving bladder outlet obstruction associated with benign prostatic hyperplasia.

< Physicochemistry>

Nonproprietary name: Tamsulosin Hydrochloride

Chemical name: 5-\{(2R)-2-[2-(2-Ethoxyphenoxy)ethylamino]propyl\}-2- methoxybenzenesulfonamide monohydrochloride

Molecular formula: $C_{20}H_{28}N_{2}O_{5}S \cdot HCl$

Molecular weight: 444.97

Melting point: About 230°C (decomposition)

Structural formula:

![Structural formula of Tamsulosin Hydrochloride]

Description:

Tamsulosin hydrochloride is a white crystal. It is freely soluble in formic acid, sparingly soluble in water, slightly soluble in acetic acid (100), and very slightly soluble in ethanol (99.5).
<Precautions for handling>

Precaution: In order to maintain quality, this product is packed in a moisture-proof inner pouch.

<Packaging>

140 tablets (14 tablets × 10) in press-through packages/Box

<References and request for literature should be made to:>

References


Distributed By:

Astellas Pharma Taiwan, Inc.
5F, No. 10, Sec. 3, Minsheng E. Rd, Taipei Taiwan

Manufactured by:

Astellas Pharma Tech Co., Ltd. Yaizu Technology Center
180 Ozumi, Yaizu-shi, Shizuoka 425-0072, Japan

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