Harnalidge® OCAS® Prolonged Release Tablets 0.4 mg
License number: 025413
Physician use only

<Qualitative and Quantitative Composition>
Each prolonged release film-coated tablet contains 0.4 mg tamsulosin hydrochloride.
Excipients: Macrogol 8,000, Macrogol 7,000,000, Magnesium Stearate, Film-coating Opadry Yellow

<Pharmaceutical Form>
Film-coated, prolonged release tablet.
(Oral Controlled Absorption System, OCAS).
Approximately 9 mm in diameter, round, bi-convex, yellow, film-coated and debossed with the code ‘04’.

<Clinical Particulars>
Indication
Low urinary tract symptoms associated with benign prostatic hyperplasia.

<Posology and Method of Administration>
The adult should be given an initial dose of tamsulosin 0.2 mg, one tablet daily. If efficacy is not sufficient at 0.2 mg, the dosage can be adjusted to Harnalidge® OCAS® 0.4 mg. Oral use, one tablet daily.
The tablet must be swallowed whole and not be crunched or chewed as this interferes with the prolonged release of the active substance.
Harnalidge® OCAS® 0.4 mg will be better to take under empty stomach due to the food will increase its exposure.
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. Such patients are not recommended to use the product due to higher content per unit dose.
No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see Contraindications)
There is no relevant indication for use of Harnalidge® OCAS® 0.4 mg in children.
**Contraindications**
Hypersensitivity to tamsulosin hydrochloride or to any of the excipients.
A history of orthostatic hypotension.
Severe hepatic insufficiency.

**Precautions and special notice for use**
As with other $\alpha_1$-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnalidge® OCAS® 0.4 mg, 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 Harnalidge® OCAS® 0.4 mg, the patient should be advised to avoid the possibility of injury resulted from syncope.

Before therapy with Harnalidge® OCAS® 0.4 mg is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

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. 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. IFIS may lead to increased procedural complications during 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 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.

Tamsulosin is mainly metabolized by CYP3A4 and CYP2D6, Harnalidge® OCAS® 0.4 mg should not be used concomitantly with CYP3A potent inhibitor (ex. ketoconazole).

**Interaction with other medicinal products and other forms of interaction**
Interaction studies have only been performed in adults.
No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. 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 posopogy need not be adjusted. 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.

No interactions at the level of hepatic metabolism have been seen during in vitro studies with liver microsomal fractions (representative of the cytochrome P450-linked drug metabolizing enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.

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

**Pregnancy and lactation**
Not applicable, as Harnalidge® OCAS® 0.4 mg is intended for male patients only.

**Effects on ability to drive and use machines**
No studies in the effects on the ability to drive and use machines have been performed. However, patients should be aware of the drowsiness, blurred vision, dizziness and syncope.
### Undesirable effects

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Common (&gt;1/100, &lt;1/10)</th>
<th>Uncommon (&gt;1/1,000, &lt;1/100)</th>
<th>Rare (&gt;1/10,000, &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous systems disorders</td>
<td>Dizziness (1.3%)</td>
<td>Headache</td>
<td>Syncope</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td></td>
<td>Rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td></td>
<td>Constipation, diarrhea, nausea, vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash, pruritus, urticaria</td>
<td>Angioedema</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Abnormal ejaculation</td>
<td>Priapism</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Asthenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As with other $\alpha_1$-adrenoceptor antagonists that could lead to drowsiness, blurred vision, thirsty and edema.

During cataract surgery, small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of tamsulosin during post-marketing surveillance. (see Special Warnings and Precautions for use)

**Overdose**

Acute overdose with 5 mg of tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed, which were treated with fluid replacement and the patient could be discharged the same day.
In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help then volumeexpanders and, when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measure be applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins. Measure, 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 administered.

<Pharmacological Properties>
Pharmacodynamic properties

Pharmacotherapeutic group
α1-adrenoceptor antagonists

Mechanism of action
tamsulosin binds selectively and competitively to the postsynaptic α1-adrenoceptor, in particular to subtypes α1A and α1D. It brings about relaxation of prostatic and urethral smooth muscle.

Pharmacodynamic effects
Harnalidge® OCAS® 0.4 mg increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra thereby improving voiding symptoms. It also improves the storage symptoms in which bladder instability plays an important role. These effects on storage and voiding symptoms are maintained during long-term therapy. The need for surgery or catheterization is significantly delayed. α1-adrenoceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with Harnalidge® OCAS® 0.4 mg.

Pharmacokinetic properties
Concentration of tamsulosin in plasma
The 16 healthy subjects with oral single-dose tamsulosin by crossover were given Harnalidge® D 0.2 mg, Harnalidge® OCAS® 0.4 mg, Harnalidge® OCAS® 0.4 mg (fed state) or 2 tablets of Harnalidge® D 0.2 mg. The relevant pharmacokinetic parameters are shown as following Table.
Absorption

Harnalidge® OCAS® 0.4 mg is a prolonged release tablet of the non-ionic gel matrix type. The OCAS formulation provided consistent slow release of tamsulosin, resulting in an adequate exposure, with little fluctuation, over 24 hours.

Tamsulosin administered as Harnalidge® OCAS® 0.4 mg is absorbed from the intestine. Of the administered dose, approximately 57% is estimated to be absorbed. After a single dose of Harnalidge® OCAS® 0.4 mg in the fasted state, plasma concentrations of tamsulosin peak at a median time of 6 hours. In steady state, which is reached by day 4 of multiple dosing, plasma concentrations of tamsulosin peak at 4 to 6 hours, in the fasted and fed state. Peak plasma concentrations increase from approximately 6 ng/mL after the first dose to 11 ng/mL in steady state. As a result of the prolonged release characteristics of Harnalidge® OCAS® 0.4 mg the trough concentration of tamsulosin in plasma amounts to 40% of the peak plasma concentration under fasted and fed conditions.

There is a considerable inter-patient variation in plasma levels both after single and multiple dosing.

Distribution

In man, tamsulosin is about 99% bound to plasma proteins. The volume of distribution is small. (about 0.2 L/kg).

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Harnalidge® D 0.2 mg (n=16)</th>
<th>Harnalidge® OCAS® 0.4 mg (n=16)</th>
<th>Harnalidge® OCAS® 0.4 mg (fed state)</th>
<th>Harnalidge® D 2 x 0.2 mg (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng x hr/mL)</td>
<td>82.5 ± 10.9</td>
<td>108.1 ± 52.7</td>
<td>177.1 ± 78.4</td>
<td>196.3 ± 120.9</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng x hr/mL)</td>
<td>90.7 ± 11.1</td>
<td>115.6 ± 53.4</td>
<td>186.1 ± 78.3</td>
<td>204.1 ± 122.4</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>7.1 ± 0.7</td>
<td>5.2 ± 2.5</td>
<td>12.0 ± 4.3</td>
<td>14.7 ± 5.9</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;*</td>
<td>4.5 (3.0-8.0)</td>
<td>6.0 (1.0-14.0)</td>
<td>7.0 (4.0-14.0)</td>
<td>4.5 (3.6-6.0)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>9.7 ± 0.86</td>
<td>10.3 ± 4.4</td>
<td>9.6 ± 2.8</td>
<td>9.5 ± 2.5</td>
</tr>
</tbody>
</table>

*: Median (Minimum value ~ Maximum value)
**Biotransformation**
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.
In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.
None of the metabolites are more active than the original compound.

**Elimination**
tamsulosin and its metabolites are mainly excreted in the urine. The amount excreted as unchanged active substance is estimated to about 4-6% of the dose, administered as Harnalidge® OCAS® 0.4 mg.
After a single dose of Harnalidge® OCAS® 0.4 mg and in steady state, elimination half-lives of about 10 and 15 hours, respectively, have been measured.

**<Clinical Studies>**
The efficacy of Harnalidge® OCAS® 0.4 mg has been evaluated in 2 randomized, placebo-controlled studies: the phase 2 dose-response study 617-CL-303 and the phase 3 study 617-CL-307. A total of 2,962 patients were studied, of which 560 were treated with 0.4mg of Harnalidge® OCAS® and 564 were treated with placebo. The remaining subjects were treated with 0.4mg (capsules), 0.8mg and 1.2mg (tablets) doses of tamsulosin hydrochloride.

**Inclusion Criteria**
In both studies the inclusion criteria were: male patients aged ≥ 45 years, diagnosed as having lower urinary tract symptoms (LUTS) suggestive of BPH, with voiding/obstructive symptoms (including incomplete emptying of the bladder, intermittency, poor stream or hesitancy), and/or storage/irritative/filling symptoms (including daytime frequency, urgency or nocturia).

These patients had a total International Prostate Symptom Score (I-PSS) of ≥ 13, both at enrolment (Visit 1) and at baseline after the 2-week placebo run-in period (Visit 2). At enrolment, they also had to have a maximum flow rate (Qmax) of ≥ 4.0 mL/s and ≤ 12.0 mL/s, with a voided volume ≥ 120 mL during free flow.

Patients with cardiac ischemia were excluded from participation in these trials. Safety in such patients has not been formally assessed.
The primary efficacy parameter in both studies following Harnalidge® OCAS® 0.4 mg treatment was the change from baseline to endpoint in total I-PSS scores. The secondary efficacy analyses contained the changes from baseline in voiding and storage I-PSS sub-scores etc.

**Study 617-CL-303**

Study 617-CL-303 was a multi-center, double-blind, randomized, placebo-controlled, parallel group, dose–response study. In this study, 211 patients received placebo and 203 patients received Harnalidge® OCAS® 0.4 mg once daily for 12 weeks of the double-blind randomized treatment. The results of study 617-CL-303 are summarized in following Table.

Results from clinical trial 617-CL-303 showing mean (SD) changes from baseline scores following daily treatment with placebo or Harnalidge® OCAS® 0.4 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Baseline Mean (SD)</th>
<th>Endpoint mean (SD)</th>
<th>Mean change (SD)</th>
<th>Mean difference vs placebo (95% CI)</th>
<th>P value vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total I-PSS</td>
<td>Placebo</td>
<td>17.8 (4.0)</td>
<td>11.7 (6.1)</td>
<td>-6.0 (5.4)</td>
<td>-1.6 (-2.5, -0.6)</td>
<td>0.0016*</td>
</tr>
<tr>
<td></td>
<td>Harnalidge® OCAS®</td>
<td>18.0 (4.3)</td>
<td>10.4 (5.5)</td>
<td>-7.6 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voidsing I-PSS</td>
<td>Placebo</td>
<td>10.4 (3.2)</td>
<td>6.9 (4.1)</td>
<td>-3.6 (3.5)</td>
<td>-1.2 (-1.9, -0.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harnalidge® OCAS®</td>
<td>10.6 (3.3)</td>
<td>5.7 (3.6)</td>
<td>-4.8 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage I-PSS</td>
<td>Placebo</td>
<td>7.3 (2.6)</td>
<td>4.9 (2.7)</td>
<td>-2.4 (2.9)</td>
<td>-0.3 (-0.8, 0.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harnalidge® OCAS®</td>
<td>7.4 (2.7)</td>
<td>4.6 (2.7)</td>
<td>-2.8 (2.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = statistically significant
I-PSS = International Prostate Symptom Score.
SD = Standard Deviation and CI = Confidence Interval
** = Odds ratio

**Study 617-CL-307**

Study 617-CL-307 was a multi-center, double-blind, randomized, placebo and active-controlled, parallel group study. In this study, 353 patients received placebo and 357 patients received Harnalidge® OCAS® once daily for 12 weeks of the double-blind randomized treatment. The results of study 617-CL-307 are summarized in following Table.
Results from clinical trial 617-CL-307 showing mean (SD) changes from baseline scores following daily treatment with placebo or Harnalidge® OCAS® 0.4 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Baseline Mean (SD)</th>
<th>Endpoint mean (SD)</th>
<th>Mean change (SD)</th>
<th>Mean difference vs placebo (95% CI)</th>
<th>P value vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total I-PSS</td>
<td>Placebo</td>
<td>18.3 (4.5)</td>
<td>12.4 (6.4)</td>
<td>-5.8 (5.6)</td>
<td>-1.7 (-2.5, -1.0)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>Harnalidge® OCAS®</td>
<td>18.5 (4.4)</td>
<td>10.8 (6.2)</td>
<td>-7.7 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voiding I-PSS</td>
<td>Placebo</td>
<td>10.6 (3.4)</td>
<td>7.0 (4.1)</td>
<td>-3.7 (3.8)</td>
<td>-1.0 (-1.5, -0.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harnalidge® OCAS®</td>
<td>10.7 (3.4)</td>
<td>6.0 (4.2)</td>
<td>-4.7 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage I-PSS</td>
<td>Placebo</td>
<td>7.6 (2.6)</td>
<td>5.4 (3.0)</td>
<td>-2.2 (2.7)</td>
<td>-0.7 (-1.1, -0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harnalidge® OCAS®</td>
<td>7.8 (2.6)</td>
<td>4.8 (2.8)</td>
<td>-3.0 (2.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = statistically significant
I-PSS = International Prostate Symptom Score.
SD = Standard Deviation and CI = Confidence Interval
** = Odds ratio

Study HAURO-0606-TW

Study HAURO-0606-TW was a single center, open-label, randomized, 3-arm parallel and active controlled treatment study in Taiwan. In this study, 23 patients received Harnalidge® OCAS® 0.4 mg, 21 patients received Harnalidge® D 0.2 mg and 21 patients received 2 tablets of Harnalidge® D once daily for 12 weeks of the treatment. The means of baseline I-PSS total score were 18.7, 18.1 and 18.8. The patients received the Harnalidge® OCAS® 0.4 mg, Harnalidge® D 0.2 mg, and 2 tablets of Harnalidge® D at week 12 weeks, the mean reductions of I-PSS total score were 5.0, 6.6 and 4.8 and the reductions of 3 group were similar, the mean reduction of I-PSS storage subscore were 1.8, 1.6 and 0.9, and the mean reductions of I-PSS voiding subscore were 3.2, 5.0 and 3.9, and the mean reductions of nocturia criterion were 0.7, 0.4 and 0.2, respectively.

Preclinical Safety Data

Single and repeat dose toxicity studies were performed in mice, rates and dogs. In addition, reproduction toxicity in rats, carcinogenicity in mice and rats and in vivo and in vitro genotoxicity were examined.

The general toxicity profiles, as seen with high doses of tamsulosin, is consistent with the known Pharmacological actions of the α-adrenoceptor antagonists.

At very high dose levels the ECG was altered in dogs. This response is considered to be not clinically relevant. Tamsulosin showed no relevant genotoxic properties.

Increased incidences of proliferative changes of mammary glands of female rates and
mice have been reported. These findings, which are probably mediated by hyperprolactinemia and only occurred at high dose levels, are regarded as irrelevant.

**Special precautions for Storage**
Store below 30℃

**Packaging**
2~1000 tablets, Alu Blister/boxes

**Expiration Date**
See the expiration date on the out-package

**Manufactured by :**
Astellas Pharma Europe B.V.
(o) Elisabethhof 19, 2353 EW Leiderdorp, Netherlands
(P) Hogemaat 2, 7942 JG Meppel, Netherlands

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