Harnal® OCAS 0.4 mg Tablet

PHARMACEUTICAL FORM

Each prolonged release film-coated tablet contains 0.4 mg tamsulosin hydrochloride.
Approximately 9 mm in diameter, round, bi-convex, yellow, film-coated and debossed with the code '04'.

INDICATIONS

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

CONTRA-INDICATIONS

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

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

As with other alpha$_1$-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal® OCAS 0.4 mg, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared.
Before therapy with Harnal® 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 and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after operation. Discontinuing tamsulosin hydrochloride 1-2 week prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery.
The initiation of therapy with tamsulosin in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assesment, surgeons and ophtalmic teams should consider whether patients scheduled for cataract or glaucoma 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 hydrocloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.
Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.

Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride.
It is possible that a remnant of the tablet is observed in the faeces.

INTERACTION WITH OTHER MEDICAL 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 or theophylline.
Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, while furosemide a fall, but as levels remain within the normal range posology 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 metabolising enzyme system), involving amitriptyline, salbutamol, glibenclamide and finasteride.
Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.
Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin hydrochloride. Concomitant administration with ketokenazole (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. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.
Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.
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, but these increases are not considered clinically relevant.
Concurrent administration of other α1-adrenoceptor antagonists could lead to hypotensive effects.

PREGNANCY AND LACTATION

Not applicable, as Harnal® OCAS 0.4 mg is intended for male patients only.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be aware of the fact that dizziness, drowsiness, blurred vision and syncope can occur.

UNDESIRABLE EFFECTS

MedDRA system organ class	**Common (>1%, <10%)**	**Uncommon (>0.1%, <1%)**	**Rare (>0.01%, <0.1%)**	**Very rare (<0.01%)**
Cardiac disorders		Palpitations		
Gastro-intestinal disorders		Constipation, diarrhoea, nausea, vomiting		
General disorders and administration site conditions		Asthenia		
Nervous systems disorders	Dizziness (1.3%)	Headache	Syncope	
Reproductive system and breast disorders	Ejaculation disorders			Priapism
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	Angioedema	Stevens-Johnson syndrome,
Vascular disorders		Orthostatic hypotension		

Respiratory, thoracic and mediastinal disorder:
Incidence unknown: Epistaxis

Gastrointestinal disorders:
Incidence unknown: Dry mouth

Skin and subcutaneous tissue disorder:
Incidence unknown: Erythema multiforme, Dermatitis exfoliative

Eye disorder:
Incidence unknown: Vision blurred, Visual impairment

During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported during post-marketing surveillance. As with other alpha-blocker and drowsiness can occur.

Post-marketing experience: In addition to the adverse events listed above, atrial fibrillation, arrhythmia, tachycardia and dyspnoea have been reported in assocation with tamsulosin use.

Because these spontaneously reported events are from the worldwide post marketing experience, the frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

OVERDOSE

Symptoms

Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

Treatment

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 volume expanders and, when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied.Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

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 administered.

POSOLOGY AND METHOD OF ADMINISTRATION

One tablet daily.

Harnal® OCAS 0.4 mg can be taken independently of food.

The tablet must be swallowed whole and not be crunched or chewed as this interferes with the prolonged release of the active substance.

Paediatric population

There is no relevant indication for use of Harnal® Ocas 0,4 mg in children.

The safety and efficacy of tamsulosin in children <18 years have not been established.

PHARMACODYNAMIC PROPERTIES

1) Pharmacotherapeutic group

α_1-adrenoceptor antagonists.

2) Mechanism of action

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

3) Pharmacodynamic effects

Harnal® 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 catheterisation 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 Harnal® OCAS 0.4 mg.

PHARMACOKINETIC PROPERTIES

1) Absorption

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

Tamsulosin hydrochloride administered as Harnal® OCAS 0.4 mg is absorbed from the intestine. Under fasting conditions approximately 57% of the administered dose is estimated to be absorbed.

The rate and extent of absorption of tamsulosin hydrochloride administered as prolonged release tablets are not affected by a low fat meal. The extent of absorption is increased by 64% and 149% (AUC and Cmax respectively) by a high-fat meal compared to fasted

Tamsulosin shows linear pharmacokinetics.

After a single dose of Harnal® 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 Harnal® 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.

2) Distribution

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

3) Metabolism

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 metabolised in the liver.

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

In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin hydrochloride metabolism by other CYP isoenzymes. Inhibition of CYP3A4 and CYP2D6 drug metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride.

None of the metabolites is more active than the original compound.

4) Excretion

Tamsulosin and its metabolites are mainly excreted in the urine. The amount excreted as unchanged active substance is estimated to be about 4 - 6% of the dose, administered as Harnal® OCAS 0.4 mg.

After a single dose of Harnal® OCAS 0.4 mg and in steady state, elimination half-lives of about 19 and 15 hours, respectively, have been measured.

No dose adjustment is warranted in renal impairment.

PRECLINICAL SAFETY DATA

Single and repeat dose toxicity studies were performed in mice, rats 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 profile, 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 rats and mice have been reported. These findings, which are probably mediated by hyperprolactinemia and only occurred at high dose levels, are regarded as irrelevant.

PACKAGING

Harnal® OCAS 0.4 **mg Tablet:**

Box of 3 x 10 Tablets

Store below 30° C.

Shelf Life: 3 years

"Harus dengan resep dokter"

No.Reg.

Manufactured by:

Astellas Pharma Europe B.V. The Netherlands.

Imported by:

PT. Combiphar, Bandung, Indonesia.

INFORMASI UNTUK PASIEN

Harnal® OCAS

400 mikrogram tablet salut film, lepas lambat

Tamsulosin hidroklorida

Bacalah leaflet ini dengan seksama sebelum anda mengkonsumsi obat ini karena berisi informasi yang sangat penting untuk anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya lagi.
- Jika anda memiliki pertanyaan lebih lanjut, silahkan menghubungi dokter, apoteker atau perawat anda
- Obat ini diresepkan hanya untuk anda. Jangan memberikan kepada orang lain. Hal tersebut mungkin dapat membahayakan mereka, walaupun tanda gejala dan penyakit mereka sama dengan anda
- Jika anda mengalami efek samping segera hubungi dokter, apoteker atau perawat anda. Termasuk jika anda mengalami efek samping yang tidak tercantum dalam leaflet ini. Lihat nomor 4

Apa saja yang terdapat dalam leaflet ini:

1. Apa itu Harnal® OCAS dan digunakan untuk apa

Apa itu Harnal® OCAS

Harnal® OCAS mengandung zat aktif tamsulosin hidroklorida. Dia bekerja dengan merelaksasi otot-otot di prostat dan uretra (tabung yang membawa urin keluar), dan membuat urin keluar lebih mudah dan membantu buang air kecil.

Pada kelenjar prostat, kandung kemih dan uretra terdapat sel khusus yang mengandung reseptor alpha 1_A yang menyebabkan otot di dalam urin mengencang. Harnal® OCAS merupakan penghambat alpha 1_A-adrenoseptor, dimana mengurangi aksi dari sel khusus dan merelaksasi otot-otot sehingga membuat pengeluaran urin lebih mudah.

Harnal® OCAS digunakan untuk apa

Harnal® OCAS digunakan untuk mengobati gejala yang berkaitan dengan *benign prostatic hiperplasia* (BPH) dimana terjadi pembesaran kelenjar prostat. Gejala ini termasuk kesulitan untuk mengeluarkan urin, menyebabkan seringnya ke toilet untuk buang air kecil, menimbulkan perasaan tidak tuntas dalam berkemih dan menyebabkan sering bangun di malam hari untuk buang air kecil.

2. Apa yang perlu diketahui sebelum menggunakan Harnal® OCAS

Jangan menggunakan Harnal® OCAS jika anda

- **Alergi** terhadap **tamsulosin atau zat lain yang terkandung dalam Harnal® OCAS** (dapat dilihat pada nomor 6)
- Mempunyai **kerusakan hati yang berat**
- Pernah **pingsan** atau merasa **pusing ketika duduk atau berdiri secara tiba-tiba**. Pusing seringkali dapat terjadi ketika mengkonsumsi Harnal® OCAS, terutama jika anda juga mengkonsumsi penghambat alpha1 lainnya. Jika anda merasa lemas atau pusing segera duduk atau berbaring hingga gejala tersebut menghilang

Peringatan dan perhatian
Bicarakan dengan dokter anda sebelum menggunakan Harnal® OCAS

- Jika anda memiliki gangguan ginjal
- Jika anda sedang menjalani atau telah dijadwalkan untuk operasi mata karena kekeruhan lensa (katarak) atau peningkatan tekanan di mata (glaukoma)

Harap informasikan dokter spesialis mata anda jika anda sebelumnya telah menggunakan, sedang menggunakan atau berencana akan menggunakan tamsulosin hidroklorida. Dokter spesialis mata kemudian dapat mengambil tindakan pencegahan yang tepat sehubungan dengan pengobatan dan teknik bedah yang akan digunakan. Tanyakan kepada dokter anda apakah anda harus menunda atau menghentikan sementara penggunaan Harnal® OCAS ketika menjalani operasi mata karena kekeruhan lensa (katarak) atau peningkatan tekanan di mata (glaukoma).

Anak dan remaja
Jangan berikan obat ini kepada anak atau remaja dibawah umur 18 tahun karena data khasiat dan keamanan untuk populasi ini belum tersedia.

Obat-obatan lain dan Harnal® OCAS
Informasikan kepada dokter atau apoteker anda jika anda sedang menggunakan atau baru saja akan menggunakan obat-obatan lain. Hal ini karena Harnal® OCAS dapat mempengaruhi cara kerja obat-obatan lain dan beberapa obat dapat mempengaruhi cara kerja dari Harnal® OCAS.

Informasikan kepada dokter atau apoteker anda khususnya jika anda sedang menggunakan:

- NSAID seperti diklofenak
- Antikoagulan seperti warfarin
- Antijamur seperti ketokonazol
- Antidepresan seperti paroxetin

Informasikan kepada dokter bahwa anda menggunakan Harnal® OCAS sebelum menjalani operasi atau tindakan pada gigi karena ada kemungkinan bahwa obat anda dapat mengganggu efek dari anestesi.

Kehamilan, menyusui dan kesuburan
Harnal® OCAS tidak digunakan untuk wanita.

Pada laki-laki, telah dilaporkan ketidaknormalan ejakulasi (penyakit ejakulasi). Hal ini berarti air mani tidak meninggalkan tubuh melalui uretra, namum masuk kedalam kandung kemih (ejakulasi mundur) atau volume ejakulasi berkurang atau tidak ada (kegagalan ejakulasi). Fenomena ini tidak berbahaya.

Mengemudi dan menggunakan mesin
Tidak tersedia informasi apakah Harnal® OCAS mempengaruhi kemampuan menyetir atau menggunakan mesin atau peralatan. Namun, dapat diketahui bahwa Harnal® OCAS dapat menyebabkan mengantuk, pandangan tidak jelas, pusing dan pingsan. Jika anda mengalami hal ini jangan mengendarai atau menggunakan mesin.

3. Bagaimana cara menggunakan Harnal® OCAS

Gunakan selalu obat ini seperti yang dokter, apoteker atau perawat anda sarankan. Periksa dengan dokter, apoteker atau perawat anda jika tidak yakin. Dosis yang disarankan untuk dewasa dan orang tua adalah satu tablet setiap hari.
Dapat digunakan bersama atau tanpa makanan. Telan tablet seluruhnya. Jangan di hancurkan atau dikunyah. Dokter anda mungkin akan memeriksa anda dari waktu ke waktu selama anda menggunakan obat ini.

Jika anda menggunakan Harnal® OCAS lebih banyak dari yang seharusnya
Jika anda menggunakan tablet lebih banyak, segera hubungi dokter anda atau pergi ke unit gawat darurat terdekat dengan membawa sisa obat dan leaflet ini.

Jika anda lupa menggunakan Harnal® OCAS
Anda dapat menggunakan pada hari yang saya jika anda lupa untuk menggunakannya. Jika anda lupa menggunakan sehari sebelumnya, lanjutkan penggunaan pada hari berikutnya. Jangan menggunakan dosis ganda untuk menutupi dosis yang terlupa.

Jika anda mempunyai pertanyaan lebih lanjut mengenai penggunaaan obat ini, tanyakan pada dokter, apoteker atau perawat anda.

4. Kemungkinan efek samping yang dapat terjadi

Seperti halnya obat lain, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Hentikan penggunaan obat ini dan konsultasikan segera dengan dokter anda jika mengalami hal-hal dibawah – anda mungkin memerlukan pengobatan khusus.

Umum terjadi (>1%, <10%)
- Pusing
- Ketidaknormalan ejakulasi

Tidak umum terjadi (>0.1%, <1%)
- Jantung berdebar
- Sulit buang air besar

- Diare
- Mual
- Muntah
- Lemas
- Sakit kepala
- Radang selaput hidung
- Ruam
- Rasa gatal
- Biduran
- Hipotensi ortostatik

Jarang terjadi (>0.01%, <0.1%)
- Kehilangan kesadaran
- Pembengkakan kulit

Sangat jarang terjadi (<0.01%)
- Ereksi terus menerus
- Sindrom *Stevens-Johnson*

Angka kejadian tidak diketahui
- Mimisan (keluar darah dari hidung)
- Mulut kering
- Lesi / luka / bintik kemerahan
- Bintik kemerahan hampir di seluruh tubuh
- Penglihatan tidak jelas
- Tidak dapat melihat

Kejadian setelah obat berada dipasar
- Ketidaknormalan ritme detak jantung
- Detak jantung tidak beraturan
- Detak jantung terlalu cepat
- Kesulitan bernafas

Jika digunakan bersamaan dengan obat serupa, dapat menyebabkan mengantuk.

Pelaporan efek samping

Jika anda mengalami efek samping, segera hubungi dokter, apoteker atau perawat anda. Hal ini termasuk kemungkinan efek samping yang tidak tercantum pada leaflet ini. Dengan melaporkan efek samping yang terjadi, anda dapat membantu memberikan informasi lebih lanjut mengenai kemanan obat ini.

5. Bagaimana cara menyimpan Harnal® OCAS

Jauhkan dari pandangan dan jangkauan anak.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum pada dus (*Expiry date*). Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan pada suhu 30°C dalam kemasan asli.

Jangan membuang obat ini melalui saluran air atau saluran pembuangan lainnya. Tanyakan pada apoteker anda bagaimana cara membuang obat yang sudah tidak digunakan. Hal ini dapat membantu dalam melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa yang terkandung dalam Harnal® OCAS

Zat aktifnya adalah tamsulosin hidroklorida. Setiap tablet lepas lambat mengandung 400 mikrogram tamsulosin hidroklorida yang setara dengan 367 mikrogram tamsulosin.

Zat tambahan lainnya adalah macrogol, magnesium stearat, butylhydroxytoluene, hypromellose dan yellow iron oxide E172.

Seperti apa tampilan Harnal® OCAS dan isi dari kemasannya

Tablet Harnal® OCAS berbentuk bulat, berwarna kuning dengan tercetak '04'.

Tablet ini tersedia dalam kemasan blister berisi 30.

"HARUS DENGAN RESEP DOKTER"

NO. Reg.

Pemegang izin edar dan produsen

Pemegang izin edar

PT. Combiphar untuk PT. Astellas Pharma Indonesia
Jl. Raya Simpang 383, Padalarang 40553,
Jawa Barat, Indonesia

Produsen

Astellas Pharma Europe B.V.
Hogemaat 2, Meppel, NL-7942-JG,
Belanda.

Untuk informasi lebih lanjut mengenai obat ini, harap menghubungi:
PT. Astellas Pharma Indonesia
Website: www.astellas.co.id