Adutasin Hard Capsule 0.5mg/0.4mg

1. NAME OF THE MEDICINAL PRODUCT
Adutasin Hard Capsule 0.5mg/0.4mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 0.5mg Dutasteride and 0.4mg Tamsulosin Hydrochloride (equivalent to 0.367mg Tamsulosin).

Excipients with known effect: Each capsule contains lecithin (which may contain soya oil) and sunset yellow FCF (E 110). Each capsule contains ≤ 0.1 mg sunset yellow FCF. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard Capsule.
Orange cap and brown body hard capsules containing white to off white pellets and one yellow soft gelatin capsule with an oily and yellowish liquid.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Adutasin treats and prevents progression of benign prostatic hyperplasia (BPH) through alleviating symptoms, reducing prostate size (volume), improving urinary flow rate and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery.

4.2. Posology and method of administration
Where appropriate, Adutasin may be used to substitute concomitant dutasteride and tamsulosin hydrochloride in existing dual therapy to simplify treatment.

Where clinically appropriate, direct change from dutasteride or tamsulosin hydrochloride monotherapy to Adutasin may be considered.

Adult males (including elderly)
The recommended dose of Adutasin is one capsule taken orally approximately 30 minutes after the same meal each day (see **"5.2. Pharmacokinetic properties - Absorption"**).

Capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.

Patients should be advised that Adutasin should not be taken on an empty stomach as this may increase the potential for cardiovascular related adverse events such as orthostatic hypotension (see **"5.1. Pharmacodynamic properties"**).

Renal impairment
The effect of renal impairment on dutasteride-tamsulosin pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see **"5.2. Pharmacokinetic properties - Renal impairment"**).

Hepatic impairment

The effect of hepatic impairment on dutasteride-tamsulosin pharmacokinetics has not been studied (see **"4.4. Special warnings and precautions for use"** and **"5.2. Pharmacokinetic properties – Hepatic impairment"**).

Adutasin is contraindicated in patients with severe hepatic impairment.

4.3. Contraindications

Adutasin is contraindicated in:

- patients with known hypersensitivity to dutasteride, other 5-alpha-reductase inhibitors (5-ARI), tamsulosin hydrochloride or any component of the formulation
- patients with a history of orthostatic hypotension
- patients with severe hepatic impairment (Child-Pugh scores >9)
- patients with severe renal impairment (creatinine clearance less than 10 mL/min)
- combination with another α-1 adrenergic blocker

Adutasin is contraindicated for use in women and children (see **"4.6. Fertility, pregnancy and lactation"**).

4.4. Special warnings and precautions for use

Adutasin should be prescribed after careful benefit risk assessment and after consideration of alternative treatment options including monotherapies.

Prostate cancer

In a 4-year study of over 8,000 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline prostate specific antigen (PSA) between 2.5 ng/mL and 10.0 ng/mL (REDUCE study), 1,517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group (n=29, 0.9 %) compared to the placebo group (n=19, 0.6 %). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers. No causal relationship between dutasteride and high-grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking dutasteride should be regularly evaluated for prostate cancer risk including PSA testing.

In an additional 2-year follow-up study with the original patients from the dutasteride chemoprevention study (REDUCE), a low rate of new prostate cancers was diagnosed (dutasteride [n=14, 1.2 %] and placebo [n=7, 0.7 %]), with no new identified cases of Gleason 8–10 prostate cancers.

Long-term follow up (up to 18 years) of another 5-ARI (finasteride) in a chemoprevention study showed no statistically significant difference between finasteride and placebo in the rates of overall survival (HR 1.02, 95 % CI 0.97-1.08) or survival after prostate cancer diagnoses (HR 1.01, 95 % CI 0.85-1.20).

Whether the effect of 5-ARIs to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. The relationship between dutasteride and high-grade prostate cancer is not clear.

Prostate specific antigen

PSA concentration is an important component of the screening process to detect prostate cancer. Dutasteride causes a decrease in mean serum PSA levels by approximately 50 % after 6 months of treatment.

Patients receiving Dutasteride/Tamsulosin Hydrochloride should have a new PSA baseline established after 6 months of treatment with dutasteride. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on Dutasteride/Tamsulosin Hydrochloride may signal the presence of prostate cancer or non-compliance to therapy with Dutasteride/Tamsulosin Hydrochloride and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-ARI (see **"Clinical Studies"**). In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with Dutasteride/Tamsulosin Hydrochloride does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established.

Total serum PSA levels return to baseline within 6 months of discontinuing treatment.

The ratio of free to total PSA remains constant even under the influence of dutasteride. If clinicians elect to use percent-free PSA as an aid in the detection of prostate cancer in men undergoing Dutasteride/Tamsulosin Hydrochloride therapy, no adjustment to its value is necessary.

Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with Dutasteride/Tamsulosin Hydrochloride and periodically thereafter.

Cardiovascular adverse events
In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤1%) and variable between the studies. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see **"Clinical Studies"**).

In a meta-analysis of 12 randomised, placebo- or comparator-controlled clinical studies (n=18,802) that evaluated the risks of developing cardiovascular adverse events from the use of dutasteride (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1.05; 95% CI 0.71, 1.57), acute myocardial infarction (RR 1.00; 95% CI 0.77, 1.30) or stroke (RR 1.20; 95% CI 0.88, 1.64) were found.

Breast cancer
There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-ARIs (see **"Clinical Studies"**). Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. It is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

Orthostatic hypotension
As with other alpha-1 adrenergic blockers, orthostatic hypotension can occur in patients treated with tamsulosin, which in rare cases can result in syncope.

Patients beginning treatment with Dutasteride should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness and vertigo) until the symptoms have resolved.

Caution is advised when alpha adrenergic blocking agents including tamsulosin are co-administered with phosphodiesterase type 5 (PDE5) inhibitors. Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension (see **"4.5. Interaction with other medicinal products and other forms of interaction"**).

Intraoperative Floppy Iris Syndrome
Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients treated with alpha-1 adrenergic blockers, including tamsulosin. IFIS may increase the risk of eye complications during and after the operation.

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

Discontinuing tamsulosin 1 to 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 (see **"4.8. Undesirable effects"**).

Leaking capsules
Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water (see **"4.6. Fertility, pregnancy and lactation"**).

Inhibitors of CYP3A4 and CYP2D6
Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 (e.g. ketoconazole), or to a lesser extent, with strong inhibitors of CYP2D6 (e.g. paroxetine) can increase tamsulosin exposure (see **"4.5. Interaction with other medicinal products and other forms of interaction"**). Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor (e.g. erythromycin), a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

Hepatic impairment
The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolised and has a half-life of three to five weeks, caution should be used in the administration of dutasteride to patients with liver disease (see **"4.2. Posology and method of administration"** and **"5.2. Pharmacokinetic properties"**).

Mood alterations and depression
Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with another oral 5-ARI. Patients should be advised to seek medical advice if any of these symptoms occur (see **"4.8. Undesirable effects"**).

Excipients
This medicinal product contains the colouring agent sunset yellow (E-110), which may cause allergic reactions.

This medicinal product contains lecithin derived from soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

4.5. Interaction with other medicinal products and other forms of interaction
There have been no drug interaction studies for Adutasin. The following statements reflect the information available on the individual components.

Dutasteride
In vitro drug metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4.

Phase II data showed a decrease in clearance of dutasteride when co-administered with the CYP3A4 inhibitors verapamil (37%) and diltiazem (44%). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride. A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10-times the recommended dose has been given to patients for up to 6 months), therefore no dose adjustment is necessary.

In vitro, dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6.

Dutasteride neither inhibits human cytochrome P450 drug-metabolising enzymes *in vitro* nor induces cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A in rats and dogs *in vivo.*

In vitro studies demonstrate that dutasteride does not displace warfarin, acenocoumarol, phenprocoumon, diazepam, or phenytoin from plasma protein, nor do these model compounds displace dutasteride. Compounds that have been tested for drug interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant pharmacokinetic or pharmacodynamic interactions have been observed.

Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in large phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase type V inhibitors, and quinolone antibiotics.

Tamsulosin
There is a theoretical risk of enhanced hypotensive effects when tamsulosin hydrochloride is co-administered with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other alpha-1 adrenergic blockers. Dutasteride/Tamsulosin Hydrochloride should not be used in combination with other alpha-1 adrenergic blockers.

Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8 respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a strong CYP3A4 inhibitor. The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure (see **"4.4. Special warnings and precautions for use"**).

Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every 6 hours for 6 days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be exercised when Dutasteride/Tamsulosin Hydrochloride is used in combination with cimetidine.

A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

In three studies, no interactions were seen when tamsulosin hydrochloride (0.4 mg/day for seven days followed by 0.8 mg/day for seven days) was given concomitantly with atenolol, enalapril or nifedipine for 3 months; therefore, no dose adjustments are necessary when these drugs are co-administered with Dutasteride/Tamsulosin Hydrochloride.

Concomitant administration of tamsulosin hydrochloride (0.4 mg/day for two days, followed by 0.8 mg/day for five to eight days) and a single intravenous (IV) dose of theophylline (5 mg/kg) resulted in no change in the pharmacokinetics of theophylline; therefore, no dose adjustment is necessary.

Concomitant administration of tamsulosin hydrochloride (0.8 mg/day) and a single IV dose of furosemide (20 mg) produced an 11% to 12 % reduction in the C_{max} and AUC of tamsulosin hydrochloride, however these changes are expected to be clinically insignificant, and no dose adjustment is necessary.

4.6. Fertility, pregnancy and lactation

There have been no studies to investigate the effect of Adutasin on pregnancy, lactation and fertility. The following statements reflect the information available on the individual components

Fertility

Dutasteride

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all time points

remained within the normal ranges and did not meet predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of the effect of dutasteride on semen characteristics for an individual patient's fertility is not known.

Tamsulosin
Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Pregnancy
Adutasin is contraindicated for use by women.

Dutasteride
Dutasteride has not been studied in women because pre-clinical data suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman exposed to dutasteride (see **"5.3. Preclinical safety data"**).

Tamsulosin
Administration of tamsulosin hydrochloride to pregnant female rats and rabbits at higher than the therapeutic dose showed no evidence of foetal harm.

Lactation
Adutasin is contraindicated for use in women.

It is not known whether dutasteride or tamsulosin are excreted in breast milk.

4.7. Effects on ability to drive and use machines
There have been no studies to investigate the effect of Adutasin on the ability to perform tasks that require judgement, motor or cognitive skills. However, patients are to be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Adutasin.

4.8. Undesirable effects
There have been no clinical trials conducted with Adutasin; however, co-administration information is available from CombAT (Combination of Dutasteride and Tamsulosin) study, a comparison of dutasteride 0.5mg and tamsulosin hydrochloride 0.4mg once daily for four years as co-administration or as monotherapy.

Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) is also provided.

Adverse drug reactions are listed below by MedDRA system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), and not known (cannot be estimated from the available data).

Dutasteride and Tamsulosin Co-administration
Clinical Trial Data

The following investigator-judged drug-related adverse events (with a cumulative incidence of greater than or equal to 1%) have been reported during CombAT study.

Adverse Reaction	Incidence during treatment period			
	Year 1	Year 2	Year 3	Year 4
Combination[a] (n) Dutasteride Tamsulosin	(n=1610) (n=1623) (n=1611)	(n=1428) (n=1464) (n=1468)	(n=1283) (n=1325) (n=1281)	(n=1200) (n=1200) (n=1112)
Impotence[b] Combination Dutasteride Tamsulosin	 6% 5% 3%	 2% 2% 1%	 <1% <1% <1%	 <1% <1% 1%
Altered (decreased) libido[b] Combination Dutasteride Tamsulosin	 5% 4% 2%	 <1% 1% <1%	 <1% <1% <1%	 0% 0% <1%
Ejaculation disorders[b] Combination Dutasteride Tamsulosin	 9% 1% 3%	 1% <1% <1%	 <1% <1% <1%	 <1% <1% <1%
Breast disorders[c] Combination Dutasteride Tamsulosin	 2% 2% <1%	 <1% 1% <1%	 <1% <1% <1%	 <1% <1% 0%
Dizziness Combination Dutasteride Tamsulosin	 1% <1% 1%	 <1% <1% <1%	 <1% <1% <1%	 <1% <1% 0%

[a] Combination = dutasteride 0.5 mg once daily plus tamsulosin hydrochloride 0.4 mg once daily.

[b] These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.

[c] Includes breast tenderness and breast enlargement.

Dutasteride Monotherapy

Clinical Trial Data

In three phase III placebo-controlled studies of dutasteride (n=2167) treatment compared to placebo (n=2158), investigator-judged drug-related adverse events after 1 and 2 years of therapy were similar in type and frequency to those observed in the dutasteride monotherapy arm of CombAT study (see table above).

No change in the adverse event profile was apparent over a further 2 years in an open-label extension phase of these studies.

Post-marketing Data

Frequency categories determined from post-marketing data refer to reporting rate rather than true frequency.

System Organ Class	Adverse reaction(s)	Frequency
Immune system disorders	Allergic reactions, including rash, pruritus, urticaria,	Very rare

	localised oedema, angioedema	
Psychiatric disorders	Depressed mood (see Warnings and Precautions)	Very rare
Reproductive system and breast disorders	Testicular pain, testicular swelling	Very rare
Skin and subcutaneous tissue disorders	Alopecia (primarily body hair loss), hypertrichosis	Rare

Tamsulosin Monotherapy

Clinical Trial Data and Post-marketing Data

The adverse reactions and frequency categories below are based on information available in the public domain. In the table below, common and uncommon reactions are consistent with those identified in a clinical trial setting and the frequency categories generally reflect incidence over placebo. Rare and very rare reactions are consistent with those identified from post-marketing reports and the frequency categories reflect reporting rates.

System Organ Class	**Frequency**			
	Common	Uncommon	Rare	Very rare
Cardiac disorders		Palpitations		
Gastrointestinal disorders		Constipation Diarrhoea Vomiting		
General disorders and administration site conditions		Asthenia		
Immune system disorders		Rash Pruritus Urticaria	Angioedema	Stevens-Johnson syndrome
Nervous system disorders	Dizziness		Syncope	
Reproductive system and breast disorders	Abnormal ejaculation			Priapism
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Vascular disorders		Postural hypotension		

During post-marketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha-1 adrenergic blocker therapy; including tamsulosin (see **"4.4. Special warnings and precautions for use"**).

Post-marketing experience: In addition, atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative and dry mouth have been reported in association with tamsulosin use.

4.9. Overdose

No data are available with regard to overdosage of Adutasin. The following statements reflect the information available on the individual components.

Dutasteride
In volunteer studies single doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In clinical studies doses of 5 mg/day have been administered to patients for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

There is no specific antidote for dutasteride therefore, in cases of suspected overdosage, symptomatic and supportive treatment should be given as appropriate.

Tamsulosin
In case of acute hypotension occurring after overdosage with tamsulosin hydrochloride cardiovascular support should be given. Restoration of blood pressure and normalization of heart rate may be accomplished by lying the patient down. If this is inadequate, administration of volume expanders and if necessary vasopressors should be used. Renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit in removing tamsulosin from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: G04C A52

Mechanism of action
Adutasin is a combination of two drugs with complementary mechanisms of action to improve symptoms in patients with BPH: dutasteride, a dual 5-alpha reductase inhibitor (5-ARI) and tamsulosin hydrochloride, an antagonist of α1a-adrenoreceptors.

Dutasteride inhibits both type 1- and type 2-, 5-alpha reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.

Tamsulosin inhibits α1a- adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75 % of the α1-receptors in the prostate are of the α_{1a} subtype.

Pharmacodynamic effects
The pharmacodynamic effects of Adutasin as a fixed dose combination would not be expected to be different from those of dutasteride and tamsulosin co-administered as separate components.

Dutasteride
Dutasteride lowers DHT levels, reduces prostate volume, improves lower urinary tract symptoms and urine flow and reduces the risk of AUR and BPH-related surgery.

The maximum effect of daily doses of dutasteride on the reduction on DHT is dose-dependent and is observed within 1 to 2 weeks. After 1 week and 2 weeks of daily dosing of dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 0.5 mg of dutasteride daily, the median decrease in DHT was 94% at 1 year and 93% at 2 years and the median increase in serum testosterone was 19% at both 1 and 2 years. This is an expected consequence of 5-alpha-reductase inhibition and did not result in any known adverse events.

Tamsulosin

Tamsulosin increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role. Alpha-1 adrenergic blockers can reduce blood pressure by lowering peripheral resistance.

The tamsulosin component in Dutasteride/Tamsulosin Hydrochloride has not been shown to be bioequivalent to tamsulosin OCAS 0.4mg. The clinical efficacy of the two tamsulosin formulations has been shown to be similar. Due to differences in pharmacokinetics, small differences in some adverse event rates have been reported. When the tamsulosin OCAS 0.4mg was compared to a tamsulosin formulation equivalent to Dutasteride/Tamsulosin Hydrochloride (tamsulosin MR 0.4mg), the incidences of all treatment emergent adverse events attributable to α1 adrenergic blockade were 6.9% (non-cardiovascular 4.4% and cardiovascular 2.5%) for the OCAS formulation and 7.8% (non-cardiovascular 5.1% and cardiovascular 3.2%) for the MR formulation. Non-cardiovascular events included all abnormal ejaculation-related events, headache, asthenia, fatigue, somnolence, rhinitis, nasal dryness, nasal congestion and nasal obstruction. Cardiovascular events included all dizziness-related events, palpitations, tachycardia, hypotension, orthostatic hypotension, dizziness postural, syncope, orthostatic/circulatory collapse and depressed level of/loss of consciousness. The most common treatment emergent adverse events were dizziness (1.4% vs 1.3%) and retrograde ejaculation (1.7% vs 1.4%). If switching between tamsulosin formulations, patients should be advised of these differences and monitored accordingly. Patients should also be reminded to adhere to the dosage and administration requirements for each product.

5.2. Pharmacokinetic properties

Bioequivalence was demonstrated between dutasteride-tamsulosin and concomitant dosing with separate dutasteride and tamsulosin capsules.

The single dose bioequivalence study was performed in both the fasted and fed states. A 30% reduction in C_{max} was observed for the tamsulosin component of dutasteride-tamsulosin in the fed state compared to the fasted state. Food had no effect on AUC of tamsulosin.

Absorption

Dutasteride

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 0.5 mg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours.

Absolute bioavailability in man is approximately 60% relative to a 2-hour intravenous infusion. The bioavailability of dutasteride is not affected by food.

Tamsulosin

Tamsulosin hydrochloride is absorbed from the intestine and is almost completely bioavailable. Tamsulosin hydrochloride exhibits linear kinetics, following single and multiple dosing, with achievement of steady state concentrations by the fifth day of once-a-day dosing. The rate of absorption of tamsulosin hydrochloride is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking tamsulosin hydrochloride approximately 30 minutes after the same meal each day.

Distribution

Dutasteride

Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma proteins (greater than 99.5%).

Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months. Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at 6 months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

Tamsulosin
The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body.

Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL).

Metabolism
Dutasteride
In vitro, dutasteride is metabolized by the human cytochrome P450 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolised by CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.

In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The five human serum metabolites of dutasteride have been detected in rat serum, however the stereochemistry of the hydroxyl additions at the 6 and 15 positions in the human and rat metabolites is not known.

Tamsulosin
There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. *In vitro* results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolizing enzymes may lead to increased exposure to tamsulosin (see **"4.4. Special warnings and precautions for use"** and **"4.5. Interaction with other medicinal products and other forms of interaction"**). The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Elimination
Dutasteride
Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0.5 mg/day to steady state in humans, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites

comprising 39%, 21%, 7%, and 7% each of drug-related material and 6 minor metabolites (less than 5% each).

Only trace amounts of unchanged dutasteride (less than 0.1% of the dose) are detected in human urine.

At low serum concentrations (less than 3 ng/mL), dutasteride is cleared rapidly by both the concentration-dependent and concentration-independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a relatively short half-life of 3 to 9 days.

At serum concentrations, greater than 3 ng/mL, dutasteride is cleared slowly (0.35 to 0.58 L/h) primarily by linear, non-saturable elimination with terminal half-life of 3 to 5 weeks. At therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks, and following repeat dosing of 0.5 mg/day, the slower clearance dominates, and the total clearance is linear and concentration-independent. Serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Tamsulosin
Tamsulosin half-life is 5 to 7 hours. Approximately 10% is excreted unchanged in urine.

Special patient populations
No pharmacokinetic studies have been conducted on special patient populations for dutasteride-tamsulosin. The following statements reflect the information available on the individual components.

Elderly
Dutasteride
Dutasteride pharmacokinetics and pharmacodynamics were evaluated in 36 healthy male subjects aged 24 to 87 following administration of a single 5 mg dose of dutasteride. Exposure of dutasteride, represented by AUC and Cmax values, was not statistically different when comparing age groups. Half-life was not statistically different when the group aged 50 to 69 was compared to the group aged over 70, which encompasses the age of most men with BPH. No differences in drug effect as measured by DHT reduction were observed between age groups. Results indicated that no dutasteride dose-adjustment based on age is necessary.

Tamsulosin
Cross-study comparison of tamsulosin hydrochloride overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in elderly males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects aged 55 to 75 compared to subjects aged 20 to 32.

Renal impairment
Dutasteride
The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CLcr < 70$ mL/min/1.73m^2) or moderate-severe ($10 \leq CLcr < 30$ mL/min/1.73m^2) renal impairment and 6 normal subjects (CLcr > 90 mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with end stage renal disease (CLcr < 10 mL/min/1.73m^2) have not been studied.

Hepatic impairment

Dutasteride

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied (see **"4.4. Special warnings and precautions for use"**). Because dutasteride is extensively metabolised, exposure could be higher in hepatically impaired patients.

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

Clinical Studies

The following statements reflect the information available on dutasteride and tamsulosin administered separately or as co-administration therapy.

Dutasteride 0.5mg/day, tamsulosin hydrochloride 0.4mg/day or the co-administration of dutasteride 0.5mg plus tamsulosin hydrochloride 0.4mg was evaluated in 4844 male subjects with enlarged prostates (greater than or equal to 30cc) in a multi-centre, double-blind, parallel group study over 4 years.

The primary efficacy endpoint at 2 years of treatment was the level of improvement from baseline in the international prostate symptom score (IPSS). The combination of dutasteride and tamsulosin provides superior improvement in symptoms than either component alone. After 2 years of treatment, co-administration therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of -6.2 units. The adjusted mean improvements in symptom scores observed with the individual therapies were -4.9 units for dutasteride and -4.3 units for tamsulosin.

The adjusted mean improvement in flow rate from baseline was 2.4 mL/sec for co-administration therapy, 1.9 mL/sec for dutasteride and 0.9 mL/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for co-administration therapy, -1.7 for dutasteride and -1.5 for tamsulosin. These improvements in flow rate and BII were statistically significant for co-administration therapy compared to both monotherapies.

The reduction in total prostate volume and transition zone volume after 2 years of treatment was statistically significant for co-administration therapy compared to tamsulosin monotherapy alone.

The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH-related surgery. After 4 years of treatment, combination therapy significantly reduced the risk of AUR or BPH-related surgery (65.8% reduction in risk p<0.001 [95% CI: 54.7% to 74.1%]) compared to tamsulosin monotherapy. The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 11.9% for tamsulosin (p<0.001). Compared to dutasteride monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6%; the difference between treatment groups was not significant (p=0.18 [95% CI: -10.9% to 41.7%]). The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 5.2% for dutasteride.

Clinical progression was defined as a composite of worsening symptoms, IPSS, and BPH-related events of AUR, incontinence, UTI, and renal insufficiency. Combination therapy was associated with a statistically significantly lower rate of clinical progression compared with tamsulosin (p<0.001, 44.1% risk reduction [95 % CI: 33.6% to 53.0%]) after 4 years. The rates of clinical progression for combination therapy, tamsulosin, and dutasteride were: 12.6%, 21.5%, and 17.8%, respectively.

The statistically significant adjusted mean improvement in symptom scores (IPSS) from baseline was maintained from year 2 to year 4. The adjusted mean improvements in symptom scores observed were -6.3 units for combination therapy, -5.3 units for dutasteride monotherapy and -3.8 units for tamsulosin monotherapy.

After 4 years of treatment, the adjusted mean improvement in maximum urinary flow rate (Q_{max}) from baseline was 2.4 mL/sec for combination therapy, 2.0 mL/sec for dutasteride monotherapy and 0.7 mL/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Q_{max} was statistically significantly greater with combination therapy at each 6-month assessment from Month 6 to Month 48 (p<0.001). Compared with dutasteride, the adjusted mean improvement from baseline in Q_{max} was not statistically significantly different than with combination therapy (p=0.050 at Month 48).

Combination therapy was significantly superior (p<0.001) to tamsulosin monotherapy and to dutasteride monotherapy for the improvement in health outcome parameters BII and BPH-related Health Status (BHS) at 4 years. The adjusted mean improvement in BII from baseline was -2.2 units for the combination, -1.8 for dutasteride and -1.2 for tamsulosin. The adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 for dutasteride and -1.1 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 4 years of treatment was statistically significant for combination therapy compared to tamsulosin monotherapy alone.

Dutasteride

Dutasteride 0.5 mg/day or placebo was evaluated in 4325 male subjects with enlarged prostates (greater than 30 cc) in three primary efficacy 2-year multi-centre, placebo controlled, double-blind studies.

In men with BPH, dutasteride treats and prevents disease progression by reducing the risk of both (acute urinary retention) AUR and the need for surgical intervention (SI) and by providing statistically significant improvement of lower urinary tract symptoms (LUTS), Q_{max} and prostate volume relative to placebo. These improvements in LUTS, Q_{max} and prostate volume were seen through to 24 months, and LUTS and Q_{max} continued to improve for a further 2

years in open label extension studies. In addition, reductions in prostate volume were sustained for a further 2 years in open label extension studies.

Cardiac failure
In a 4-year comparison of dutasteride co-administered with tamsulosin and dutasteride or tamsulosin monotherapy in men with BPH (CombAT study), the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: dutasteride, 4/1623 (0.2%) and tamsulosin, 10/1611, (0.6%). The relative risk estimate for time to first cardiac failure event was 3.57 [95% CI: 1.17, 10.8] for combination treatment compared to dutasteride monotherapy and 1.36 [95% CI: 0.61, 3.07] compared to tamsulosin monotherapy.

In a 4-year chemoprevention comparison study of placebo and dutasteride in 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (REDUCE), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride (30/4105, 0.7%) versus placebo (16/4126, 0.4%) for a relative risk estimate for time to first cardiac failure event of 1.91 [95% CI: 1.04, 3.50].

In a post-hoc analysis of concomitant alpha blocker use, there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking dutasteride and an alpha blocker concomitantly: dutasteride and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), placebo and no alpha blocker (15/2727, 0.6%). No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see **"4.4. Special warnings and precautions for use"**).

Prostate cancer and high grade tumours
In a 4-year comparison of placebo and dutasteride in 8231 men aged 50 to 75, the REDUCE study, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (REDUCE), 6,706 subjects had prostate needle biopsy data available for analysis to determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6). There was no difference in the incidence of Gleason 7-10 cancers (p=0.81).

There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%) (p=0.15). In Years 1-2, the number of subjects with Gleason 8-10 cancers was similar in the dutasteride group (n=17, 0.5%) and the placebo group (n=18, 0.5%). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the dutasteride group (n=12, 0.5%) compared with the placebo group (n=1, <0.1%) (p=0.0035). There are no data available on the effect of dutasteride beyond 4 years in men at risk of developing prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the dutasteride group (0.5% in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5%, respectively). In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were (n=8, 0.5%) for dutasteride, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy (see **"4.4. Special warnings and precautions for use"**).

The results of an epidemiological, population-based study (n=174,895) in community practice settings show that the use of 5-ARIs to treat BPH/LUTS is not associated with an increased risk of prostate cancer mortality (hazard ratio adjusted for competing risks: 0.85, 95% CI 0.72,

1.01) when compared with the use of alpha-blockers. Similar results were reported in an epidemiological study (n=13,892) of men with prostate cancer in the UK (adjusted hazard ratio for prostate cancer mortality for 5-ARI users versus non-users: 0.86; 95% CI 0.69, 1.06). A prospective cohort study, the Health Professional's Follow-up Study (n=38,058), also found that 5-ARI use was not associated with fatal prostate cancer (adjusted HR: 0.99; 95% CI 0.58, 1.69).

Effects on prostate specific antigen and prostate cancer detection
In REDUCE study in patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL, dutasteride treatment caused a decrease in mean serum PSA by approximately 50% after 6 months of treatment with a large variability (standard deviation of 30%) among patients. PSA suppression observed at 6 months was similar in men who did or who did not develop biopsy-detectable prostate cancer during the study (see **"4.4. Special warnings and precautions for use"**).

Incidence of breast cancer
In BPH monotherapy clinical trials, providing 3374 patient years of exposure to dutasteride, there were 2 cases of male breast cancer reported in dutasteride-treated patients, one after 10 weeks and one after 11 months of treatment and 1 case in a patient who received placebo. In subsequent clinical trials in BPH and 8231 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL providing 17489 patient years exposure to dutasteride and 5027 patient years exposure to dutasteride and tamsulosin combination, there were no additional cases in any of the treatment groups.

Two case control, epidemiological studies, one conducted in a US (n=339 breast cancer cases and n=6,780 controls) and the other in a UK (n=398 breast cancer cases and n=3,930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5 ARIs (see **"4.4. Special warnings and precautions for use"**). Results from the first study did not identify a positive association for male breast cancer (relative risk for ≥ 1 year of use before breast cancer diagnosis compared with < 1 year of use: 0.70: 95% CI 0.34, 1.45). In the second study, the estimated odds ratio for breast cancer associated with the use of 5-ARIs compared with non-use was 1.08: 95% CI 0.62, 1.87).

The relationship between long-term use of dutasteride and male breast cancer has not been established.

Tamsulosin
Tamsulosin rapidly (from one week) increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role.

5.3. Preclinical safety data
Non-clinical studies have not been conducted with Adutasin. Dutasteride and tamsulosin hydrochloride individually have been extensively evaluated in animal toxicity tests and findings were consistent with the known pharmacological actions of 5-alpha-reductase inhibitors and alpha-adrenergic blockers. The following statements reflect the information available on the individual components.

Carcinogenesis/mutagenesis
Dutasteride and tamsulosin hydrochloride showed no evidence of genotoxicity in a wide range of *in vitro* and *in vivo* tests.

Dutasteride

In a carcinogenicity study in rats, dutasteride produced an increase in benign interstitial cell tumours in the testis at the high dose (158-fold clinical exposure). However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans. There were no clinically relevant effects on tumour profile in a carcinogenicity study in mice.

Tamsulosin
In carcinogenicity studies in rats and mice, tamsulosin hydrochloride produced an increased incidence of proliferative changes of the mammary glands in females. These findings, which are probably mediated by hyperprolactinaemia and only occurred at high dose levels, are regarded as not clinically relevant.

Reproductive toxicology
Dutasteride
Dutasteride produced a reversible decrease in fertility in male rats consistent with the pharmacological activity of 5-alpha-reductase inhibition on accessory reproductive organs.

This is considered to have no clinical relevance as there was no effect on sperm development, concentration or motility.

Feminisation of the external genitalia was noted in male foetuses of female rats and rabbits orally dosed with dutasteride. However, IV administration of dutasteride to pregnant Rhesus monkeys during embryofoetal development at doses of up to 2010 ng/animal/day did not produce adverse maternal or foetal toxicity. This dose represents a multiple of at least 186-fold (ng/kg basis) the potential maximum daily dose in a 50 kg woman, resulting from exposure to 5 mL semen (assuming 100% absorption) from a dutasteride-treated man.

Tamsulosin
High doses of tamsulosin hydrochloride resulted in a reversible reduction in fertility in male rats considered possibly due to changes of semen content or impairment of ejaculation. Effects of tamsulosin on sperm counts or sperm function have not been evaluated.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits at higher than the therapeutic dose showed no evidence of foetal harm.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hard Capsule Shell:
Hypromellose, Potassium Chloride, Carrageenan, Titanium Dioxide, Sunset Yellow, Red Iron Oxide

Dutasteride 0.5mg Soft Capsule:
Glycerol monocaprylocaprate, Butylhydroxytoluene, Gelatin, Glycerol, Titanium Dioxide, Yellow Iron Oxide, Triglycerides, Lecithin (soya)

Tamsulosin 0.4mg Pellet:
Microcrystalline Cellulose, Magnesium Stearate, Methacrylic acid-Ethyl acrylate copolymer, Sodium Hydroxide, Triacetin, Purified Talc, Titanium Dioxide, Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life
Please refer to expiry date on the blister strip or outer carton.

6.4. Special precautions for storage
Do not store above 30°C.

6.5. Nature and contents of container
Alu/Alu blister of 5 x 6's packed in an outer carton.

6.6. Special precautions for disposal and other handling
No special requirements.

7. PRODUCT REGISTRATION HOLDER (MALAYSIA)
Apex Pharmacy Marketing Sdn Bhd
No. 2, Jalan SS 13/5, 47500 Subang Jaya, Selangor, Malaysia.

PRODUCT REGISTRANT (SINGAPORE)
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8. MANUFACTURER
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28750 Madrid, Spain.

9. DATE OF REVISION OF THE TEXT
06/08/2026

Font size: 7pt (Times New Roman)