CHEMO

LEÓN FARMA
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1. NAME OF THE MEDICINAL PRODUCT

inTASTERIDE (Dutasteride) 0.5 mg soft gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg dutasteride. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule

Dutasteride 0.5 mg soft capsules are oblong soft gelatin capsules (approximately 16.5 x 6.5 mm) of light yellow colour, filled with transparent liquid.

4. CLINICAL PARTICULARS

▪ 4.1 Therapeutic indications

Monotherapy

inTASTERIDE is indicated for the treatment and control of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery.

Combination with Alpha-Blocker

inTASTERIDE in combination with the alpha-blocker tamslosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

▪ 4.2 Posology and method of administration

Adult males (including elderly)

Capsules should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa.

inTASTERIDE may be taken with or without food.

The recommended dose of inTASTERIDE is one capsule (0.5 mg) taken orally once a day. Although an improvement may be observed at an early stage, treatment for at least 6 months may be necessary in order to assess objectively whether a satisfactory response to the treatment can be achieved. For the treatment of BPH, inTASTERIDE can be administered alone or in combination with the alpha-blocker tamsulosin (0.4mg).

Renal impairment

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of dutasteride is contraindicated.

▪ 4.3 Contraindications

inTASTERIDE is contraindicated in:
- Patients with known hypersensitivity to the active substance, other 5-alpha reductase inhibitors, or to any of the excipients listed in section 6.1.
- Women, children and adolescents (see section 4.6).
- Patients with severe hepatic impairment.
- This medicinal product contains lecithin (may contain soya oil). If you are allergic to peanut or soya, do not use this medicinal product.

▪ 4.4 Special warnings and precautions for use

General

Lower urinary tract symptoms of BPH can be indicative of other urological diseases, including prostate cancer. Patients should be assessed to rule out other urological diseases prior to treatment with dutasteride.Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5 alpha-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

Increased Risk of High-Grade Prostate Cancer

In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).

5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study related factors, impacted the results of these studies has not been established.

Blood donation

Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Prostate specific antigen (PSA)

Serum 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 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 may signal the presence of prostate cancer or non-compliance to therapy with dutasteride and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-ARI. In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with dutasteride 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 therapy, no adjustment to its value is necessary.

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

Cardiovascular adverse events

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.

Breast cancer

There have been rare reports of male breast cancer reported in men taking Dutasteride. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

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 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease (see sections 4.2, 4.3 and 5.2).

▪ 4.5 Interaction with other medicinal products and other forms of interaction

For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection, please see section 4.4.

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.

There is 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 six months); therefore, no dose adjustment is necessary.

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

Dutasteride neither inhibits human cytochrome P450 drug-metabolizing 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, diazepam, acenocoumorol, phenprocoumon, 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.

No clinically significant adverse interactions were observed 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.

▪ 4.6 Fertility, pregnancy and lactation

Pregnancy

Dutasteride is contraindicated for use by women. 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.

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Breastfeeding

It is not known whether dutasteride is excreted in human milk.

Fertility

Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men. The possibility of reduced male fertility cannot be excluded.

▪ 4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties of dutasteride, treatment with dutasteride would not be expected to interfere with the ability to drive or operate machinery.

▪ 4.8 Undesirable effects

Dutasteride as monotherapy or in combination with tamsulosin:

The most common adverse reactions reported in subjects receiving dutasteride were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders. The most common adverse reactions reported in subjects receiving combination therapy (dutasteride plus tamsulosin) were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness.

Adverse drug reactions are listed below by system organ class and frequency.

Immune system disorders
Very rare: Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema.
Psychiatric disorders
Very rare: Depressed mood
Skin and subcutaneous tissue disorders
Rare: Alopecia (primarily body hair loss), Hypertrichosis
Reproductive system and breast disorders
Very rare: Testicular pain and testicular swelling

▪ 4.9 Overdose

Single daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. Doses of 5 mg daily have been administered to subjects 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 suspected overdose symptomatic and supportive treatment should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

▪ 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors.
ATC code: G04C B02.
Dutasteride is a dual inhibitor of 5 alpha reductase. It 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.

▪ 5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single 0.5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60%. The bioavailability of dutasteride is not affected by food.

Distribution

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (>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 (Css) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Biotransformation

In vitro, dutasteride is metabolised by the human cytochrome P450 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolized by CYP1A2, CY2A6, 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.

Elimination

Dutasteride is extensively metabolized.
Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged 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 therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks. Serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Linearity/non-linearity

Dutasteride pharmacokinetics can be described as first order absorption process and two parallel elimination pathways, one saturable (concentration-dependent) and one non-saturable (concentration independent).

At low serum concentrations (less than 3 nanograms/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 short half-life of 3 to 9 days.

At serum concentrations, greater than 3 nanograms/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, following repeat dosing of 0.5mg/day, the slower clearance dominates and the total clearance is linear and concentration-independent.

Elderly

No significant influence of age was seen on the exposure of dutasteride but the half- life was shorter in men under 50 years of age. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old.

Renal impairment

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 (see section 4.2).

Hepatic impairment

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see section 4.3).

▪ 5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

▪ 6.1 List of excipients

Capsule contents:
Propylene Glycol Monocaprylate
Butylhydroxytoluene

Capsule shell:
Bovine Gelatin
Glycerol
Titanium dioxide (E171)
Triglycerides (medium chain)
Lecithin (may contain soya oil)

▪ 6.2 Incompatibilities

Not applicable.

▪ 6.3 Shelf life

Please refer to expiry on the outer carton and blister

▪ 6.4 Special precautions for storage

Do not store above 30. Keep blister in the outer cardboard carton in order to protect from light

▪ 6.5 Nature and contents of container

Transparent Triplex (PVC-PE-PVDC)/Aluminium blister 30 and 90 capsules

▪ 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

▪ 6.7 Instructions for Use/Handling

Dutasteride is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking capsules (see section 4.6). If contact is made with leaking capsules, the contact area should be washed immediately with soap and water. Women who are pregnant or may be pregnant should not handle inTASTERIDE because of the possibility of absorption of dutasteride and the potential risk of a foetal anomaly to a male foetus

▪ 7. PRODUCT REGISTRATION HOLDER

Intega Sdn Bhd 8-08, Level 8, Menara MBMR, No. 1, Jalan Syed Putra, 58000 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur

▪ 8. MANUFACTURER

LABORATORIOS LEÓN FARMA, SA
Polígono Industrial Navatejera, C/ La Vallina s/n,
Villaquilambre, 24193 León Spain

▪ 9. DATE OF REVISION OF THE TEXT

22/06/2025

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