Applicant : Eurolab (Pty) Ltd
Proprietary name : Tasdiam 50 mg & 150 mg
Dosage form and strength : Film-coated tablets 50 mg & 150 mg
Date of submission : 01 June 2020
Approval date : 06 June 2020

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

Tasdiam 50 mg film-coated tablets

Tasdiam 150 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tasdiam 50:

Each film-coated tablet contains bicalutamide 50 mg

Contains sugar: Lactose monohydrate (62,7 mg).

Tasdiam 150:

Each film-coated tablet contains bicalutamide 150 mg

Contains sugar: Lactose monohydrate (188,0 mg).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

Tasdiam 50:

White, round, biconvex, film-coated tablets with a diameter of 6,5 mm.

Tasdiam 150:

White, round, biconvex, scored, film-coated tablets with a diameter of 10,5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tasdiam 50:

Treatment of locally advanced prostate cancer in combination with luteinising hormone releasing hormone (LHRH) analogue therapy or surgical castration.

Tasdiam 150:

In patients with locally advanced prostate cancer (T3-4, any N, MO/T1-2, N+, M0) **Tasdiam 150** is indicated either alone or as an adjuvant to treatment by radical prostatectomy or radiotherapy.

Tasdiam 150 is indicated as monotherapy for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical or medical castration is not appropriate.

4.2 Posology and method of administration

Tasdiam 50:

Adult males including the elderly

One tablet (50 mg) once a day. Treatment with **Tasdiam** should be started at least three days before commencing treatment with a LHRH analogue, or at the same time as surgical castration.

Tasdiam 150:

Adult males including the elderly

One tablet (150 mg) once a day for 2 years or until progression.

Tasdiam can be taken with or without food.

Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

Hepatic Impairment

No dosage adjustment is necessary for patients with mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe hepatic impairment (see under **Section 4.4**).

4.3 Contraindications

Women and children, or breastfeeding mothers.

Tasdiam must not be given to any patient who has shown a hypersensitivity reaction to bicalutamide or any of the ingredients of **Tasdiam**.

4.4 Special warnings and precautions for use

Hepatic function impairment

Metabolism of **Tasdiam** may be delayed in patients with moderate to severe hepatic function impairment, resulting in prolonged elimination half-life and increased risk of toxicity. Periodic assessment of hepatic function should be considered during long-term use of **Tasdiam**.

Special precautions

Tasdiam is extensively metabolised in the liver. Data suggest that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of **Tasdiam**. Therefore,

Tasdiam should be used with caution in patients with moderate to severe hepatic impairment. Periodic liver function testing should be considered due to the possibility of hepatic changes. Severe hepatic changes have been observed infrequently with **Tasdiam** (see section 4.8). **Tasdiam** therapy should be discontinued if changes are severe.

Lactose

Tasdiam contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **Tasdiam**.

Tasdiam 50

A reduction in glucose tolerance has been observed in males receiving LHRH agonists and **Tasdiam**. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving **Tasdiam** in combination with LHRH agonists.

Clinically discontinuation of **Tasdiam** can result in anti-androgen withdrawal syndrome in a subset of patients. This is characterised by a decline in PSA (prostate specific antigen) or clinical response following withdrawal of the anti-androgen component of Maximal Androgen Blockade (MAB). This syndrome has been well described in scientific literature although the pathophysiology is unknown and may reflect multiple mechanisms, but is believed to represent the development of agonistic activity by the medicine at the receptor level due to receptor mutations with advancing disease. Although this effect has only been reported with the 50 mg dose (approved for use in combination therapy), given the likely mode of action the phenomenon could theoretically occur with the 150 mg dose used as single agent therapy.

4.5 Interaction with other medicines and other forms of interaction

Luteinising hormone releasing hormone (LHRH)

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between **Tasdiam** and LHRH analogues.

Ketoconazole and cimetidine

Formal interaction studies have not been undertaken, but caution should be exercised when prescribing **Tasdiam** with other medicines, e.g. ketoconazole and cimetidine, which may inhibit oxidation of **Tasdiam**. It could result in increased plasma concentrations of **Tasdiam** which could lead to an increase in side-effects.

Medicines metabolised by Cytochrome P450

Although clinical studies using antipyrine as a marker of Cytochrome P450 (CYP) activity showed no evidence of an interaction potential with **Tasdiam** midazolam exposure (AUC) was increased by up to 80 %, after co-administration with **Tasdiam** for 28 days. Caution should be exercised with the co-administration of **Tasdiam** with medicines such as astemizole, cisapride and ciclosporin; these medicines should not be used with **Tasdiam**.

Warfarin

Tasdiam can displace warfarin, from its protein binding sites. It is, therefore, recommended that if **Tasdiam** is started in patients who are already receiving warfarin, prothrombin time/INR should be closely monitored.

4.6 Fertility, pregnancy and lactation

Tasdiam is contra-indicated in women.

4.7 Effects on ability to drive and use machines

During treatment with **Tasdiam,** somnolence has been reported and those patients who experience this symptom should not drive or use machines.

4.8 Undesirable effects

The pharmacological action of **Tasdiam** may give rise to certain expected effects. These include hot flushes, pruritus, and in addition, breast tenderness and gynaecomastia, which may be reduced by concomitant castration. **Tasdiam** may also be associated with the concurrence of diarrhoea, nausea, vomiting, asthenia and dry skin. Hepatic changes (elevated levels of transaminases, jaundice), severe, have been observed in patients treated with **Tasdiam**. The changes may be transient, resolving or improving despite continued therapy or

following cessation of therapy. Periodic liver function testing should be considered (see section 4.4). Cardiovascular effects such as angina, heart failure, conduction irregularities in PR and QT interval prolongation, dysrythmias and non-specific ECG changes have been observed. Thrombocytopenia has been observed.

The following adverse experiences were reported and arranged in system organ classes:

System Organ class	**Frequencies**	**Adverse Reaction**
Infections and infestations	Less frequent	Pulmonary and upper respiratory tract infections: bronchitis, pneumonia, sepsis.
Blood and the lymphatic system disorders	Less frequent	Anaemia
	Frequency unknown	Leucopenia, thrombocytopenia, neutropenia, haemolysis.
Immune system disorders	Less frequent	Angioedema.
Endocrine disorders	Frequent	Hot flushes.
Metabolism and nutrition disorders	Frequent	Weight gain.
	Less frequent	Oedema, weight loss.

	Frequency unknown	Diabetes, hyperglycaemia.
Psychiatric disorders	Less frequent	Reversible neurological reactions such as nervousness, insomnia, mental depression, confusion, dizziness.
	Frequency unknown	Somnolence.
Nervous system disorders	Less frequent	Chills, headache, drowsiness
Eye disorders	Less frequent	Visual disturbances including chromatopsia and impaired adaptation or increased sensitivity to light.
Cardiac disorders	Frequent	Myocardial infarction (fatal outcomes have been reported), Cardiac failure
	Less frequent	Angina, heart failure, dysrhythmias and ECG changes such as PR and QT interval prolongation.
Vascular disorders	Less frequent	Hypertension.
Respiratory, thoracic and mediastinal disorders	Frequent	Runny nose, cough or hoarseness, fever, shortness of breath, dyspnoea and tightness of chest or wheezing, sore throat, chest pain, pulmonary disorders such as pulmonary fibrosis, pneumonia or pneumonitis.
	Less frequent	Interstitial lung disease (Fatal outcomes have been reported).

Gastro-intestinal disorders	Frequent	Diarrhoea, constipation, nausea
	Less frequent	Gastro-intestinal or rectal bleeding, dryness of mouth, bloated feeling, flatulence, indigestion, dyspepsia, vomiting, loss of appetite.
Hepato-biliary disorders	Less frequent	Hepatic failure Fatal outcomes have been reported
	Frequency unknown	Methaemaglobinaemia, hepatitis or jaundice, cholestatic jaundice, elevated levels of transaminases.
Skin and subcutaneous tissue disorders	Frequent	Pruritus, alopecia, dry skin.
	Less frequent	Skin rash, rash, itching of skin, epidermal necrolysis.
	Frequency unknown	Sweating, hirsutism.
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle and joint weakness, neuropathy, muscle weakness in hands, arms, feet and legs.
Renal and urinary disorders	Less frequent	Haematuria.
	Frequency unknown	Nocturia.
Reproductive system and breast disorders	Frequent	Gynaecomastia, decreased libido, impotence, breast tenderness, galactorrhoea.
General disorders and administration site conditions	Frequent	Asthenia.
	Less frequent	Chills, headache, chest pain, fever, flu-like symptoms.

	Frequency unknown	Abdominal pain, pain, pelvic pain, hypersensitivity reactions including rash.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no human experience of overdosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since **Tasdiam** is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Bicalutamide is a non-steroidal anti-androgen, devoid of other endocrine activity. Regression of prostatic tumours results from this inhibition. Bicalutamide is a racemate with its anti-androgenic activity being almost exclusively in the (R)-enantiomer.

5.2 Pharmacokinetic properties

Bicalutamide is well absorbed following oral administration. There is no evidence of any clinical relevant effect of food on bioavailability. Bicalutamide is highly plasma protein bound and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal portions.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Povidone K – 25

Sodium starch glycolate

opadry OY-S-9622

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 25 ºC. Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

28 or 30 film-coated tablets (2 blister strips of 14 tablets each or 3 blister strips of 10 tablets each) are packed in transparent PVC/PVDC/Aluminium blisters. The blisters are subsequently packed into cardboard boxes.

6.6 Special precautions for disposal and other handling

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue

Woodmead

2144

8 REGISTRATION NUMBER

Tasdiam 50: 44/21.12/1022

Tasdiam 150: 44/21.12/1023

9 DATE OF FIRST AUTHORISATION

19 April 2013

10 DATE OF REVISION OF THE TEXT

06 June 2020