SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Casodex Tablets 50 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg bicalutamide (INN).

3. PHARMACEUTICAL FORM

White film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

4.2 Posology and method of administration

Adult males including the elderly: one tablet (50 mg) once a day.

Treatment with Casodex should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Children: Casodex is contraindicated in children.

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 Section 4.4).

4.3 Contraindications

Casodex is contra-indicated in females and children (see section Pregnancy and lactation). Casodex must not be given to any patient who has shown a hypersensitivity reaction to the active substance or to any of the excipients of this product.

Co-administration of terfenadine, astemizole or cisapride with Casodex is contra-indicated.

4.4 Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of a specialist.
Casodex 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 Casodex. Therefore, Casodex 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. The majority of changes are expected to occur within the first 6 months of Casodex therapy.

Severe hepatic changes and hepatic failure have been observed rarely with Casodex and fatal outcomes have been reported (see Section 4.8). Casodex therapy should be discontinued if changes are severe.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. 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 Casodex in combination with LHRH agonists.

Casodex has been shown to inhibit cytochrome P450 (CYP 3A4), as such, caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4, see Sections 4.3 and 4.5.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Androgen deprivation therapy may prolong the QT interval.
In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Casodex.

**Laboratory Tests**
Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response. If PSA levels rise during CASODEX therapy, the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of antiandrogen, while continuing the LHRH analog, may be considered.

**4.5 Interaction with other medicaments and other forms of interaction**

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between Casodex and LHRH analogues. In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a drug interaction potential with Casodex, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of Casodex for 28 days. For drugs with a narrow therapeutic index such an increase could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contra-indicated and caution
should be exercised with the co-administration of Casodex with compounds such as ciclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporin, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of Casodex therapy. Caution should be exercised when prescribing Casodex with other drugs which may inhibit drug oxidation eg, cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of Casodex which theoretically could lead to an increase in side effects.

In vitro studies have shown that Casodex can displace the coumarin anticoagulant, warfarin, from its protein binding sites. It is therefore recommended that if Casodex is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Casodex with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

### 4.6 Pregnancy and lactation

Casodex is contra-indicated in females and must not be given to pregnant women or nursing mothers.

### 4.7 Effects on ability to drive and use machines

Casodex is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.

### 4.8 Undesirable effects

In this section, undesirable effects are defined as follows: 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); very rare (≤1/10,000); not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Hypersensitivity, angioedema and urticaria</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Decreased libido</td>
</tr>
<tr>
<td>Disorder Category</td>
<td>Frequency</td>
<td>Common Conditions</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-----------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Myocardial infarction (fatal outcomes have been reported)&lt;sup&gt;4&lt;/sup&gt;, Cardiac failure&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>QT prolongation (see sections 4.4 and 4.5).</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very common</td>
<td>Hot flush</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Interstitial lung disease&lt;sup&gt;5&lt;/sup&gt;. (Fatal outcomes have been reported).</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Abdominal pain constipation</td>
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<tr>
<td></td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dyspepsia flatulence</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Common</td>
<td>Hepatotoxicity, jaundice, raised transaminases&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hepatic failure&lt;sup&gt;2&lt;/sup&gt;. Fatal outcomes have been reported.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Alopecia hirsutism/hair re-growth</td>
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<tr>
<td></td>
<td></td>
<td>dry skin</td>
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<td></td>
<td></td>
<td>pruritus</td>
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<tr>
<td></td>
<td></td>
<td>rash</td>
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<tr>
<td></td>
<td>Rare</td>
<td>Photosensitivity reaction</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Very common</td>
<td>Gynaecomastia and breast tenderness&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oedema</td>
</tr>
</tbody>
</table>
1. Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
2. Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of hepatic failure in patients receiving treatment in the open-label Casodex arm of the 150 mg EPC studies.
3. May be reduced by concomitant castration.
4. Observed in a pharmaco-epidemiology study of LHRH agonists and anti-androgens used in the treatment of prostate cancer. The risk appeared to be increased when Casodex 50 mg was used in combination with LHRH agonists but no increase in risk was evident when Casodex 150 mg was used as a monotherapy to treat prostate cancer.
5. Listed as an adverse drug reaction following review of post-marketed data. Frequency has been determined from the incidence of reported adverse events of interstitial pneumonia in the randomised treatment period of the 150 mg EPC studies.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

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 Casodex 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

Antiandrogen, ATC code L02 B B03

Casodex is a non-steroidal antiandrogen, devoid of other endocrine activity. It binds to the androgen receptors without activating gene expression, and thus inhibits the androgen stimulus. Regression of prostatic tumours results from this inhibition. Clinically, discontinuation of Casodex can result in antiandrogen withdrawal syndrome in a subset of patients.

Casodex is a racemate with its antiandrogen activity being almost exclusively in the (R)-enantiomer.

5.2 Pharmacokinetic properties

Casodex is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.
The (S)-enantiomer is rapidly cleared relative to (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week.

On daily administration of Casodex, the (R)-enantiomer accumulates about 10-fold in plasma as a consequence of its long half-life.

Steady state plasma concentrations of the (R)-enantiomer, of approximately 9 micrograms/ml are observed during daily administration of 50 mg doses of Casodex. At steady state, the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. There is evidence that for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.

Casodex is highly protein bound (racemate 96%, (R)-bicalutamide 99.6%) and extensively metabolised (via oxidation and glucuronidation); its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

In a clinical study the mean concentration of R-bicalutamide in semen of men receiving Casodex 150 mg was 4.9 microgram/ml. The amount of bicalutamide potentially delivered to a female partner during intercourse is low and by extrapolation possibly equates to approximately 0.3 microgram/kg. This is below that required to induce changes in offspring of laboratory animals.

5.3 Pre-clinical safety data

Casodex is a potent antiandrogen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction, in animals, are related to these activities. None of the findings in the preclinical testing is considered to have relevance to the treatment of advanced prostate cancer patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Casodex includes the following excipients:

Lactose Monohydrate, Magnesium Stearate, methylhydroxypropyl cellulose, Macrogol 300, Povidone, Sodium starch glycolate, Titanium Dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Special precautions for storage

Do not store above 25°C.

6.4 Presentation

Packs of 28 tablets.
6.5 Instructions for use and handling

No special precautions required.

7. REGISTRATION NUMBER

103 82 28597 00.

8. MANUFACTURER

AstraZeneca UK Limited, Cheshire, England

9. IMPORTER

AstraZeneca Israel Ltd, POB 4070, Raanana 4366241

Date of Revision: July 2015

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