**Core Safety Profile**

Drug Substance Bicalutamide

Date 20 December 2011

# CASODEX Core Safety Profile

# 1. INTRODUCTION

The Core Safety Profile (CSP) for CASODEX has been generated following the 2008 EU PSUR Work Sharing Scheme and any new information that has been added to the Company Core Data Sheet during the intervening period.

Notes for reading the text:
*Text in italics should only be included in products containing lactose*
Underlined text should only be included in SPCs for bicalutamide 150 mg
**Bold text should only be included in bicalutamide 50 mg**
Any text in green highlight has been added since the 2008 Final CSP.

# 2. CASODEX CORE SAFETY PROFILE

## 4.3 Contraindications

Bicalutamide is contraindicated in females and children (see Section 4.6).

Bicalutamide 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 Bicalutamide is contraindicated (see section 4.5).

## 4.4 Special warnings and precautions for use

Initiation of treatment should be under the direct supervision of a specialist. [this may not apply to all EU member states]

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

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

For patients who have an objective progression of disease together with elevated PSA, cessation of bicalutamide therapy should be considered.

**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 bicalutamide in combination with LHRH agonists.**

Bicalutamide 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.*

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

**There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide 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 bicalutamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of bicalutamide 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 contraindicated (see section 4.3) and caution should be exercised with the co-administration of bicalutamide 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 bicalutamide therapy.

Caution should be exercised when prescribing bicalutamide with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide which theoretically could lead to an increase in side effects.

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

## 4.6 Pregnancy and lactation

Bicalutamide is contraindicated in females and must not be given to pregnant women or nursing mothers.

## 4.7 Effects on ability to drive and use machines

Bicalutamide 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 form the available data).

**Table 1 Frequency of Adverse Reactions**

| System Organ Class | Frequency | CASODEX 150 mg (monotherapy) | CASODEX 50 mg (+ LHRH analogue) |
|---|---|---|---|
| Blood and Lymphatic system disorder | Very common | | **Anaemia** |
| | Common | Anaemia | |
| Nervous System Disorders | Very common | | **Dizziness** |
| | Common | Dizziness, somnolence | **Somnolence** |
| Vascular disorders | Very common | | **Hot flush** |
| | Common | Hot flush | |
| Gastrointestinal disorders | Very common | | **Abdominal pain, constipation, nausea** |
| | Common | Abdominal pain, constipation, dyspepsia, flatulence, nausea | **Dyspepsia, flatulence** |
| Skin and subcutaneous tissue disorders | Very common | Rash | |
| | Common | Alopecia, hirsutism/ hair re-growth, dry skin[1], pruritus | **Alopecia, hirsutism/ hair re-growth, rash, dry skin, pruritus** |
| Renal and urinary disorders | Very common | | **Haematuria** |
| | Common | Haematuria | |
| Reproductive system and breast disorders | Very common | Gynaecomastia and breast tenderness[a] | **Gynaecomastia and breast tenderness[b]** |

**Table 1 Frequency of Adverse Reactions**

| System Organ Class | Frequency | CASODEX 150 mg (monotherapy) | CASODEX 50 mg (+ LHRH analogue) |
|---|---|---|---|
| | Common | Erectile dysfunction | **Erectile dysfunction** |
| General disorders and administration site conditions | Very common | Asthenia | **Asthenia, oedema** |
| | Common | Chest pain, oedema | **Chest pain** |
| Metabolism and nutrition disorders | Common | Decreased appetite | **Decreased appetite** |
| Psychiatric disorders | Common | Decreased libido, depression | **Decreased libido, depression** |
| Cardiac disorders | Common | | **Myocardial infarction (fatal outcomes have been reported)[g] ,Cardiac failure[g]** |
| Hepatobiliary disorders | Common | Hepatotoxicitiy, jaundice, hypertransaminasaemia[c] | **Hepatotoxicitiy, jaundice, hypertransaminasaemia[c]** |
| | Rare | Hepatic failure[f] (fatal outcomes have been reported) | **Hepatic failure[f] (fatal outcomes have been reported)** |
| Investigations | Common | Weight increased | **Weight increased** |
| Immune system disorders | Uncommon | Hypersensitivity, angioedema, and urticaria | **Hypersensitivity, angioedema, and urticaria** |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Interstitial lung disease[e] (fatal outcomes have been reported) | **Interstitial lung disease[e] (fatal outcomes have been reported)** |

[a] The majority of patients receiving CASODEX 150 mg as monotherapy experience gynaecomastia and/or breast pain. In studies these symptoms were considered to be severe in up to 5% of the patients. Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment.

[b] **May be reduced by concomitant castration.**

[c] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.

[d] Due to the coding conventions used in the EPC studies, adverse events of 'dry skin' were coded under the COSTART term of 'rash'. No separate frequency descriptor can therefore be determined for the 150 mg CASODEX dose however the same frequency as the 50 mg dose is assumed.

[e] 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.

[f] 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.

[g] 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.

~~In addition, cardiac failure was reported in clinical trials (as a possible adverse drug reaction in the opinion of investigating clinicians, with a frequency of >1%) during treatment with bicalutamide plus an LHRH analogue. There is no evidence of a causal relationship with drug treatment.~~

## 4.9 Overdose

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