AstraZeneca

EU RMP

Drug Substance	Bicalutamide
Version Number	2
Date	2 May 2014

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI: 2 ELEMENTS FOR A PUBLIC SUMMARY

Bicalutamide (CASODEX™[1]) is a hormonal therapy anticancer agent, used for the treatment of prostate cancer. Hormones are chemical messengers that help to control the activity of cells or organs. Hormonal therapies work by interfering with the production or action of hormones in the body. CASODEX has a chemical structure similar to a group of hormones that are found at higher levels in males than females (called 'androgen' or 'male' hormones; the most important and well-known of which is testosterone).

Prostate cancer cells need a supply of hormones such as testosterone to grow. These hormones get into the cancer cell and attach to a type of protein called a receptor. CASODEX attaches to the same receptors as testosterone and blocks the effect of testosterone on the prostate cancer cells. Without testosterone, the cancer cells either grow more slowly or stop growing altogether. The cancer may shrink in size as a result.

Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of CASODEX has been established

VI:2.1 Overview of disease epidemiology

Prostate cancer is a disease in which malignant (cancerous) cells form in the prostate gland. The risk of developing of prostate cancer varies between countries; In Europe, 17 to 62 men in every 100,000 men are diagnosed with the disease per year. Risk increases with age, and most men are older than 65 years when first diagnosed. Risk is higher in some ethnic groups and is also affected by diet and body weight.

Many cases of prostate cancer are slow-growing and only need regular monitoring (watchful waiting). Treatment is needed when the cancer is fast-growing or spreads to areas just outside the prostate (locally-advanced disease) or to other areas of the body (advanced or metastatic disease). Treatment may include surgery to remove the testicles, or chemotherapy, including hormonal therapies. With treatment, over 7 in 10 men with advanced prostate cancer survive for 5 years or more.

[1] CASODEX is a trademark of the AstraZeneca group of companies.

VI:2.2 Summary of treatment benefits

CASODEX, at a dose of 50 mg per day was studied in over 800 men with advanced prostate cancer and compared with a similar medicine called flutamide. All patients also received injections of another medicine, to block the production of luteinising hormone. Treatment benefits were maintained for significantly longer in men in the CASODEX group compared with men in the flutamide group, who were 34% more likely to fail treatment over the study period.

The results of a further 2 studies in over 1400 men with prostate cancer given CASODEX alone at a dose of 150 mg per day, showed that men without metastatic disease who were treated with CASODEX lived as long without their disease worsening or treatment failing as men who had surgery. CASODEX was not as effective as surgery in patients with metastatic disease, but metastatic disease patients treated with CASODEX reported a better quality of life compared with patients who had surgery. CASODEX is a treatment option for men with metastatic prostate cancer who do not want, or cannot have, surgical treatment.

In early prostate cancer, adding CASODEX to standard of care was significantly better than standard of care alone, in preventing the worsening of disease.

VI:2.3 Unknowns relating to treatment benefits

CASODEX has not been studied in women and has only been studied in a small number of children. CASODEX has been studied men of different age, race and stage of cancer. Most men were White, although other ethnic groups showed no evidence of a different effect.

VI:2.4 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and important missing information, these are defined as follows:

- An important identified risk is an untoward event for which there is enough evidence for it to be linked with the medicine of interest, and where the possibility of that event occurring could lessen the potential benefits of taking the medicine
- A important potential risk is an untoward occurrence for which there is some reason for suspicion of a link with the medicine of interest but where this link has not been confirmed
- Important missing information is information about the safety of a medicine, which is not available when the medicine was approved for sale. This may represent a gap in the ability to predict the safety of the medicine on particular topics after the medicine has been approved.

Table I-1 Important identified risks

Risk	What is known	Preventability
Liver problems	CASODEX has been linked to a range liver problems, ranging from mild changes in liver function test results to serious, potentially-fatal events such as liver failure. More than 1 in 10 men, but less than 1 in 100 men treated with CASODEX have had liver problems. Most changes in liver function were mild and of short duration. The risk factors for developing liver problems during CASODEX treatment include: men with existing liver diseases such as hepatitis caused by infection, complications resulting in a lack of blood supply to the liver, or by an autoimmune disease; men with cirrhosis (scarring) or blockage of the bile duct, men who are alcoholics; men with an inflamed liver due to non-alcoholic fatty liver disease and men taking other drugs or substances known to affect the liver. Additionally, a number of inherited diseases may increase the risk of developing liver problems during CASODEX treatment. These include: a condition known as alpha-1-antitrypsin deficiency which leads to the build up of alpha-1-antitrypsin in the liver; and conditions which lead to a build up of iron (haemochromatosis) or copper (Wilson's disease) in the body.	Patients and physicians should be aware of the risks of liver problems, especially in patients who may be at an increased risk of developing liver problems. CASODEX should be used with caution in men with mild to moderate liver disorders. Men with early signs and symptoms of liver problems should be investigated further. In serious cases, stopping CASODEX treatment is important to prevent further complications.
Serious inflammation of the lung called interstitial lung disease (ILD)	ILD may be caused by a number of factors, one of which is anti-cancer drug treatment. ILD is difficult to diagnose, but if untreated, can be life-threatening or fatal. The ways in which anti-cancer drugs might cause ILD are not fully understood, but one possible reason is that anti-cancer agents reduce the ability of body to respond to lung injury. The development of ILD during CASODEX treatment has been reported as occurring in less than 1 in 100 men.	Patients and physicians should be aware of the risks of ILD. Any CASODEX-treated patient who experiences shortness of breath, cough and fever should have treatment interrupted and be investigated for possible ILD. If ILD is found, CASODEX should be permanently stopped and the patient treated appropriately.

Table I-1 Important identified risks

Risk	What is known	Preventability
Heart failure	The chance of developing prostate cancer increases with age, as does the chance of developing heart failure. Because of this, patients receiving treatment for prostate cancer also tend to be at a higher risk of heart and blood circulation-related events such as heart failure. Heart failure has been observed in patients who received CASODEX together with another type of medicine that blocks the production of luteinising hormone. The development of heart failure during CASODEX treatment has been reported as occurring in less than 1 in 10 men but more than 1 in 100 men.	Stopping treatment with CASODEX either for a short time, or permanently, may be necessary in patients with heart failure. Damage to the heart may not be reversible upon stopping CASODEX treatment.
Heart attack (myocardial infarction)	The chance of developing prostate cancer increases with age, as does the chance of having a heart attack. Because of this, patients receiving treatment for prostate cancer also tend to be at higher risk of a heart and blood circulation-related events such as heart attack. Heart attacks during CASODEX treatment have been reported as occurring in less than 1 in 10 men but more than 1 in 100 men. Older people, males, smokers and people with diabetes, high blood pressure or high blood cholesterol levels are at an increased risk of developing a heart attack. A number of inherited factors may also increase the risk of having a heart attack.	None

Table I-2 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Male Breast Cancer	Breast cancer in men is rare, because the androgen hormones such as testosterone, which are found in high levels in males, inhibit breast growth. Hormones found in higher levels in females, such as oestrogen, promote breast growth. The risk of developing male breast cancer may already be greater in men with prostate cancer. CASODEX at a dose of 150 mg per day is known to increase the risk of developing enlarged breasts in males, by affecting the balance of male to female hormones (the testosterone to oestrogen ratio) in the body. Some rare inherited diseases and other drugs which alter the testosterone to oestrogen ratio have been shown to increase the risk of developing male breast cancer, and because of the effects of CASODEX on the balance of male to female hormones, CASODEX treatment could also increase the risk of developing male breast cancer. The risks of male breast cancer occurring as a result of CASODEX treatment are considered to be low, as even in the rare inherited diseases where the testosterone to oestrogen ratio is affected from birth male breast cancer takes several decades to develop.
Metabolic Syndrome	Metabolic syndrome is the medical term for a combination of diabetes, high blood pressure, high blood cholesterol levels and obesity. People with metabolic syndrome have a higher risk of heart disease, stroke and other conditions affecting blood vessels. Clinical studies have shown that the development of metabolic syndrome may be linked to low levels of androgen hormones. There is a potential risk for men treated with CASODEX to develop metabolic syndrome, due to the decrease in the levels of androgens caused by CASODEX treatment

Table I-3 Missing information

Risk	What is known
Not applicable	Not applicable

VI:2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics, which provides physicians, pharmacists and other health care professionals with details on how to use the medicine and any risks, and recommendations for reducing them. An easier-to-read summary of this information is provided in the form of the package leaflet. The information in these documents is known as routine risk minimisation (reduction) measures.

Some medicines have special conditions and restrictions for their safe and effective use (additional risk reduction measures). However, there are no additional risk minimisation measures for CASODEX.

VI:2.6 Planned post authorisation development plan

There are no post-authorisation development plans or further investigations of safety concerns for the use of CASODEX, for the licensed indication and no studies that are a condition of the marketing authorisation.

VI:2.7 Summary of changes to the Risk Management Plan over time

The significant changes to the EU-RMP since approval are summarised in Table I-4

Table I-4 Major changes to the Risk Management Plan over time

Version	Date *(at time of authorisation)*	Safety Concerns	Comment
1	01 June 2007	Heart attack was added as an important identified risk and heart failure was changed from a potential risk to an important identified risk.	An internal safety evaluation in response to the Dutch health authorities concluded that there was enough evidence to support a link between the use of CASODEX and the risk of having a heart attack. The same review also showed that the frequency with which heart failure was reported on CASODEX treatment needed to be changed.
		A statement that 'fatal outcomes have been observed' was added to the risks of liver problems and interstitial lung disease	Although liver problems and ILD were already identified risks with CASODEX treatment, on-going safety review processes showed that a number of these cases reported with CASODEX were fatal