VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Estrogen receptor-positive breast cancer:

Breast cancer is the most common cancer in women. Incidence rates vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. Some of the factors associated with breast cancer are female gender, age, family history, genetics, obesity, physical inactivity, alcohol or hormone replacement therapy. One type of breast cancer is estrogen receptor positive (ER+) type in which the cancer cells, like normal breast cells, may receive signals from estrogen that could promote their growth. About 75% of all breast cancers are "ER+". Breast cancer tumours that are ER+ are likely to respond to endocrine therapy. Endocrine therapies are usually taken after surgery, chemotherapy, and/or radiation. Such therapy helps prevent recurrence of the disease by blocking the effects of estrogen.[3, 5]

VI.2.2 Summary of treatment benefits

Fulvestrant is used to treat locally advanced or metastatic breast cancer in women who have been through the menopause. It is used for cancer that is 'oestrogen-receptor positive' (when the cancer cells have receptors for the hormone oestrogen on their surface). 'Locally advanced' means that the cancer has started to spread, and 'metastatic' means that the cancer has already spread to other parts of the body. Fulvestrant is used when the disease has returned during or after treatment with an 'anti-oestrogen' (a type of medicine used to treat breast cancer), or when the disease has got worse during treatment with an anti-oestrogen.

This marketing authorization is for an essentially similar Medicinal Product with the same Summary of the Product Characteristics (SmPC) as the innovator's product – Faslodex (AstraZeneca).[1]

Faslodex has been studied in three main studies involving women who had been through the menopause with advanced breast cancer that had come back or got worse after previous hormonal treatment. Two of the studies compared Faslodex taken at a dose of 250 mg once a month with anastrozole (another anticancer medicine) taken at a dose of 1 mg every day in 851

women. The third study compared two doses of Faslodex (250 and 500 mg) in 736 women. In all of the studies, the main measure of effectiveness was how long the patients lived without their disease getting worse.[6]

In the first two studies, Faslodex was as effective as anastrozole: the women receiving Faslodex lived for an average of 5.4 months without their disease getting worse, compared with 4.1 months in those taking anastrozole. In the third study, the 500-mg dose of Faslodex was more effective than the 250-mg dose: the women receiving the higher dose lived for an average of 6.5 months without their disease getting worse, compared with 5.5 months in those receiving the lower dose.[6]

If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, fulvestrant can be considered effective in the approved indication.

VI.2.3 Unknowns relating to treatment benefits

Unknowns relating to treatment benefits Limited or no information is available in the treatment of:

- paediatric population (children aged 0 to 18 years),
- patients with severe hepatic impairment,
- patients with severe renal impairment.
- use during pregnancy and breast-feeding

VI.2.4 Summary of safety concerns

Important identified risk

Risk	What is known	Preventability
Injection site reactions	Fulvestrant may cause reactions at the injection site such as pain and/or inflammation. Injection site reactions, such as pain and/or inflammation are very common side effects (may affect more than 1 in 10 people treated).	If the patients get injection site reactions, such as pain and/or inflammation, they should talk to their doctor, pharmacist or nurse.
Increased risk of bleeding at the injection site	Bruising and bleeding at the site of injection can occur due to the injection of the drug directly into a muscle (intramuscular route). Therefore, fulvestrant should be used with caution if treating patients with bleeding problems, low blood platelet count (thrombocytopenia) or those taking medicines to prevent blood clots.	The patients should tell to their doctor, pharmacist, or nurse before using fulvestrant if they have low numbers of platelets (which help blood clotting), bleeding disorders, previous problems with blood clots, or if they are using anticoagulants

Risk	What is known	Preventability
	Bruising and bleeding at the site of injection is an uncommon side effects (may affect up to 1 in 100 people treated).	(medicines to prevent blood clots). If the patients get bruising and bleeding at the site of injection, they should inform their doctor, pharmacist or nurse.
Increased risk of blood clots within a vein *[Venous thromboembolic events]*	Increased risk of blood clots (thromboembolism) is commonly seen in women with advanced breast cancer and have been observed in studies with fulvestrant (may affect up to 1 in 10 people treated with fulvestrant). However, the exact role of fulvestrant cannot be assessed since the cancer patients are at higher risk of developing venous thromboembolic events.	The patients may need immediate medical treatment if they experience thromboembolism (increased risk of blood clots). The patients should tell to their doctor, pharmacist, or nurse before using fulvestrant if they have bleeding disorders or previous problems with blood clots.
Allergic reactions *[Hypersensitivity reactions]*	Allergic reactions such as swelling of the face, lips, tongue and/or throat and itching skin and skin rash such as hives may occur with fulvestrant and may affect up to 1 in 10 people treated with fulvestrant.	The patients must not take fulvestrant if they are allergic to fulvestrant or any of the other ingredients of this medicine. The patients should tell to their doctor, pharmacist, or nurse before getting fulvestrant if they have allergic reactions, including swelling of the face, lips, tongue and/or throat. The patients should inform their doctor, pharmacist, or nurse immediately if they experience allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue and/or throat because they may need immediate medical treatment.
Liver and biliary disorder	Abnormal levels of liver enzymes (AST, ALT, ALP, in blood tests) are a very common side	Patients should consult their doctor, pharmacist or nurse

Risk	What is known	Preventability
*[*Hepatobiliary disorders*]*	effect of fulvestrant (may affect more than 1 in 10 people). Elevation of bile pigment produced by the liver (bilirubin) is a common side effect (may affect up to 1 in 10 people). Increase of gamma-GT (a liver enzyme seen in a blood test) is an uncommon side effect (may affect up to 1 in 100 people). Patients may also develop inflammation of the liver (hepatitis) and liver failure, with a frequency of up to 1 in 100 people (uncommon side effect).	before using fulvestrant if they have any liver problems. Patients with severe liver problems must not use fulvestrant. The patients should inform their doctor, pharmacist, or nurse immediately if they experience inflammation of the liver (hepatitis), or liver failure. If the patients get abnormal levels of liver enzymes, increase of bilirubin (bile pigment produced by the liver) or increase of gamma-GT (a liver enzyme seen in a blood test), they should talk to their doctor, pharmacist or nurse.

Important potential risks

Risk	What is known
Reduced bone mineral density *[Reduced bone mineral density (osteopenia) and Osteoporosis]*	There are no long-term data on the effect of fulvestrant on bone. But due to the mechanism of action of fulvestrant (estrogen blockers) there is a potential risk of bone thinning. The doctor should be informed if a patient has osteoporosis.
Foetal abnormalities and loss of pregnancy *[Reprotoxicity]*	In studies with animals, foetal abnormalities and loss of pregnancy occurred. Hence, if pregnancy occurs while taking fulvestrant, there is a potential hazard to the foetus and potential risk for loss of pregnancy. Fulvestrant must not be used if a woman is pregnant. If she can become pregnant, she should use effective methods to prevent a pregnancy while being treated with this drug.
Formation of micro-clots of oily solutions that plug the blood vessels in the lung	As the product contains castor oil as an ingredient, it must not be administered into a vein. The oily solutions must be injected strictly intramuscularly and slowly (1-2 minutes/injection). Pulmonary microembolism of oily solutions could lead to signs and symptoms such as cough, shortness of breath (dyspnoea) or chest pain. These

Risk	What is known
[Pulmonary microembolism of oily solutions]	reactions may occur during or immediately after the injection.[2-4,7-8]
Ischaemic heart and blood vessels problems *[Ischaemic cardiovascular events]*	The patients treated with fulvestrant may be at a potential risk of developing ischaemic cardiovascular events. However, the exact mechanism by which fulvestrant may cause heart problems is not well-understood.
Abnormal changes of the endometrium *[Endometrial dysplasia]*	There is possibility of abnormal changes of the inner mucous membrane of the uterus (endometrium) due to fulvestrant therapy. Animal data do not suggest that fulvestrant would have that effect on the uterus of postmenopausal women. Current data in breast cancer patients treated with fulvestrant did not result in clinically significant changes in endometrial thickness. There is no evidence of uterus thickness change in the breast cancer patients studied.
Disease that inflames or scars the lungs *[Interstitial lung disease]*	The patients treated with fulvestrant may be at a potential risk of developing interstitial lung disease. However, a mechanism by which fulvestrant might cause this event is not known.
Inflammation of blood vessels *[Vasculitis]*	The patients treated with fulvestrant may be at a potential risk of developing vasculitis. However, a mechanism by which fulvestrant might cause this event is not known.

Missing information

Risk	What is known
Use in children and adolescents	Fulvestrant is not indicated in children and adolescents under 18 years, as there is insufficient information about administration of fulvestrant in this group of patients.
Use in patients with severely decreased liver function *[Use in patients with severe hepatic impairments]*	The patients must not take fulvestrant if they have severe liver problems, since there are no data for this patient group. Fulvestrant should be used with caution in patients with mild to moderate liver problems, since the exposure may be increased. The patients should talk to their doctor, pharmacist, or nurse before getting fulvestrant if they have liver problems.

Risk	What is known
Use in patients with severe kidney impairment *[Use in patients with severe renal impairments]*	There is insufficient information regarding administration of fulvestrant in patients with severe renal impairment, therefore fulvestrant should be used with caution in these patients. The patients should talk to their doctor, pharmacist, or nurse before getting fulvestrant if they have kidney problems.

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

Summary of Product Characteristics (SmPC) of Fulvestrant SUN 250 mg solution for injection in pre-filled syringe provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL) for patients.
For all above mentioned risks, routine risk minimisation measures are given in in SmPC and PL of Fulvestrant SUN 250 mg solution for injection in pre-filled syringe and no additional risk minimisation measures are proposed for safety concerns identified with Fulvestrant SUN 250 mg solution for injection in pre-filled syringe.

VI.2.6 Planned post-authorization development plan

None.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1.0	17-Mar-17	*Important identified risks* • Injection site reactions • Increased risk of bleeding at the injection site • Venous thromboembolic events • Hypersensitivity reactions • Hepatic disorders *Important potential risks* • Osteoporosis • Foetal toxicity and loss of pregnancy • Pulmonary microembolism of oily solutions *Missing information*	New RMP issue for new NL/DCP.

Version	Date	Safety Concerns	Comment
		• Use in children and adolescents • Use in patients with severe hepatic impairments • Use in patients with severe renal impairments • Use during pregnancy and lactation	
1.1 (current)	26-Oct-2017	*Important identified risks* • Injection site reactions • Increased risk of bleeding at the injection site • Venous thromboembolic events • Hypersensitivity reactions • Hepatobiliary disorders *Important potential risks* • Reduced bone mineral density (osteopenia) and osteoporosis • Reprotoxicity • Pulmonary microembolism of oily solutions • Ischaemic cardiovascular events • Endometrial dysplasia • Interstitial lung disease • Vasculitis *Missing information* • Use in children and adolescents • Use in patients with severe hepatic impairments • Use in patients with severe renal impairments	Following day 70 Preliminary Assessment Report of RMS , NL (Procedure no: NL/H/3953/001/DC) the summary of safety concerns was updated as following: Missing information “Use during pregnancy and lactation” has been deleted. Some risks has been renamed: • The important identified risk of “hepatic disorders” was renamed as “hepatobiliary disorders” • The important potential risk of “osteoporosis” has been renamed as “reduced bone mineral density (osteopenia) and osteoporosis”. • “Foetal toxicity and loss of pregnancy” was renamed as “Reprotoxicity” *Few risks have been added as Important potential risks:* • Ischaemic cardiovascular events • Endometrial dysplasia

Version	Date	Safety Concerns	Comment
			• Interstitial lung disease • Vasculitis Part III, Part V and Part VI were also amended in line with changes performed in the summary of safety concerns. Annex 2 was updated with revised SmPC and PL.