13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Breast cancer is the most common cancer in women worldwide. The most common type of breast cancers are those stimulated by female sex hormones called oestrogens (hormone receptor-positive breast cancer). The exact cause of breast cancer is unknown. However, certain factors are known to influence the risk (risk factors) for breast cancer. The main risk factors include, being a woman, being older (most breast cancers are found in women who are 50 years old or older), and having changes in certain breast cancer genes. In addition, studies have shown that the factors listed below may also influence the risk:

- Long-term use of hormone replacement therapy;
- Personal history of breast cancer or non-cancerous breast diseases;
- Family history of breast cancer (especially in first degree relations maternal or paternal);
- Treatment with radiation therapy to the breast/chest;
- Dense breasts by mammogram;
- Drinking alcohol.

Today about 96% of women survive breast cancer for at least one year, and about 87% live for five years or more (Cancer Research UK, 2014).

13.2.2 Part VI.2.2 Summary of treatment benefits

Breast cancer is treated in several ways and often requires more than one kind of treatment. It depends on the kind of breast cancer and how far it has spread. For most women, the first treatment for breast cancer is surgery to remove it. Additional treatments, called adjuvant treatment, are usually given to reduce the risk of the cancer coming back. These treatments may include radiotherapy, chemotherapy, hormonal therapy, and targeted therapy.

Femara contains an active substance called letrozole. It belongs to a group of medicines called aromatase inhibitors. It is a hormonal breast cancer treatment. Growth of breast cancer is frequently stimulated by oestrogens which are female sex hormones. Letrozole blocks an enzyme called aromatase which is involved in the production of oestrogens. It reduces the amount of oestrogen in the body and therefore may block the growth of breast cancer that needs oestrogens to grow. As a consequence tumor cells slow or stop growing and/or spreading to other parts of the body.

Letrozole is used to treat breast cancer in women who have gone through menopause i.e, cessation of periods.

It is also used to prevent cancer from coming back. It can be used as first treatment before breast cancer surgery in case immediate surgery is not suitable or it can be used as first treatment after breast cancer surgery or following five years treatment with tamoxifen. Letrozole is also used to prevent breast tumor spreading to other parts of the body in patients with advanced breast cancer.

Treatment after breast cancer surgery (adjuvant treatment)

A large study was conducted in more than 8000 women to evaluate the use of letrozole as adjuvant therapy for post-menopausal women with hormone receptor-positive breast cancer in comparison to tamoxifen, with a median follow-up of 96 months. The results showed that 5 years of letrozole treatment is superior to tamoxifen in reducing the risk of DFS events, defined as the interval between randomization and the earliest recurrence of cancer in the same breast, spread of breast cancer to other parts of the body (distant metastasis), breast cancer in the other breast, or death from any cause. There was a 13% reduction with letrozole treated women (626 with letrozole & 698 tamoxifen) in all breast cancer related events.

Treatment before breast cancer surgery (neoadjuvant treatment)

A study was conducted in 337 postmenopausal women with primary, untreated breast cancer who did not qualify for breast-conserving surgery. These patients were randomly allocated either to receive letrozole for 4 months or tamoxifen for 4 months. On clinical assessment there were 55% objective responses in the letrozole treated group compared to 36% for the tamoxifen treated group. This finding was consistently confirmed by ultrasound (letrozole 35% versus tamoxifen 25%), and by mammography (letrozole 34% versus tamoxifen 16%). In total 45% of patients in the letrozole group versus 35% of patients in the tamoxifen group underwent breast-conserving surgery. During the 4-month pre-operative treatment period, 12% of patients treated with letrozole and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

Treatment after surgery and tamoxifen (extended adjuvant treatment

A study in more than 5100 women was conducted to assess the benefit and safety of letrozole compared with placebo for 5 years in women who had undergone surgical removal of a primary breast cancer and subsequently received ≥4.5-<6 years of adjuvant tamoxifen therapy, with a follow-up of more than 5 years.

The results showed that letrozole given within 3 months of completion of adjuvant tamoxifen treatment significantly reduced the risk of breast cancer recurrence compared with placebo. A significantly greater proportion of patients in the placebo arm (286 patients, 11.1%) had disease recurrence than in the letrozole arm (209 patients, 8.1%) translating into a relative risk reduction of 25%.

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Letrozole has been used in treatment of women with breast cancer in over 120 countries around the world. There is no evidence to suggest that benefit of letrozole treatment is different in any specific female population.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-4 Important identified risks

Risk	What is known	Preventability
Increased level of cholesterol (hypercholesterolemia)	Increased level of cholesterol is a very common side effect occurring in 10 or more women treated with letrozole. In most cases the increase is mild. A result of sustained increased level of cholesterol over time is risk of developing fatty deposits in the walls of your arteries called atheromas which if block the coronary arteries can lead to heart disease.	Appropriate dietary and exercise regimen can help prevent risk of developing clinically significant dyslipidemia and mitigate its secondary effects on cardiovascular system.
Thinning or wasting of your bones (osteoporosis), leading to bone fractures in some cases	Thinning of bones and fractures are common side effects seen in 1-10 women out of each 100 women treated with letrozole.	Careful monitoring of bone health and adequate management of bone loss using appropriate, timely treatment could prevent onset of osteoporosis and potentially reduce the risk of bone fractures.
	Elderly patients (≥ 65 years) enrollment), patients who had a prior history of osteoporosis or bone fractures have higher risk of experiencing bone fractures.	Patients who have a history of osteoporosis or bone fractures should tell their doctor so that s/he can take this into account during treatment. For e.g. bone density (a way of monitoring for osteoporosis) can be performed before, during and after treatment and appropriate timely treatment administered to prevent bone thinning and fractures.
Coronary Heart Disease (Ischemic heart disease)	Coronary heart disease is an uncommon side effect which may occur in less than one woman out of 100 women treated with letrozole. This slight increased risk however, does not cause increased death rate due to heart disease in women treated with letrozole.	Currently there are no known specific preventive measures while under treatment with letrozole. Prevention, monitoring and management of any cholesterol increase could help decrease risk of cardiac disease. In addition awareness and early recognition of clinical signs of coronary heart disease (chest pain, breathlessness etc) and seeking timely medical assistance for them can also help reduce risk of developing life threatening condition. In addition, healthy life style changes can also help reduce the risk.
Heart failure (Cardiac failure)	Cardiac failure has not been shown to be directly caused by letrozole. However, it can be occur as a consequence of severe coronary heart disease. The most vulnerable patients would be the elderly women with pre-existing heart or blood vessels disease.	Same as for coronary heart disease.

Risk	What is known	Preventability
Stroke (Cerebrovascular accidents)	Stroke or brain tissue damage due blocking of blood supply to brain is an uncommon adverse event seen in less than 1 woman out of 100 women treated with letrozole. Results from special studies confirmed that treatment with letrozole is not associated with an increased risk of cardiovascular or cerebrovascular deaths.	Same as for coronary heart disease.
Congenital malformations (birth defects)	There have been reports in the post marketing environment of congenital malformations in babies born to mothers who consumed letrozole during pregnancy.	Pre-menopausal and pregnant females should not take letrozole.
Co-administration of tamoxifen with letrozole	Tamoxifen, if administered together with letrozole reduces the beneficial effect of letrozole.	Tamoxifen should not be used together with letrozole.

Table 13-5 Important potential risks

Risk	What is known
Cancer of the gut / large intestine (Colorectal cancer)	To date it has not been established if treatment with letrozole can cause increase in cancers of the gut. Results from studies did not show any increase of gut cancers in patients treated with letrozole when compared with those who received Tamoxifen or placebo, even after more than 5 years of observation. The overall survival rate of patients with breast cancer has increased over the years largely because adjuvant therapy. With improved survival more breast cancer patients are at risk of having a new unrelated cancer. This risk can be due purely to chance occurrence as risk of all cancers increases with age. The increased risk of a new cancer could also be due to factors with shared risk for e.g. family history, environmental and lifestyle factors such as smoking, alcohol, obesity. Large studies have shown that in some cases this increase may be related to adjuvant treatment including cancers of the gut. However, the risk associated with treatment is very small. Moreover, it is not yet clear what role is played by other risk factors increasing chance of treatment related cancers. It is generally recommended for all patients after successful treatment of cancer to adopt healthy lifestyle choices such as healthy eating, exercise, cessation of smoking and alcohol, limiting UV exposure. This could help reduce risk of some of the secondary cancers.

Table 13-6 Missing information

Risk	What is known
None	-

13.3 Part VI.2.5 Summary of additional risk minimization measures by safety concern

This medicine has no additional risk minimization measures.

13.4 Part VI.2.6 Planned post authorization development plan

There is no post-authorization development plan.

13.4.1 List of studies in post authorization development plan

None.

13.4.2 Studies which are a condition of the marketing authorization

No studies are conditions of the marketing authorization.

13.5 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 13-7 Major changes to the Risk Management Plan over time

RMP Version	RMP Date	Safety Concerns	Comment
2	30-Sep-2007	Not applicable.	
3	12-Feb-2015	Colorectal cancer, defined as an important identified risk in previous RMP, is now categorized as an important potential risk.	Based on the review of the current safety data from 2 pivotal studies (BIG 1-98 and MA-17). It was assessed to categorize colorectal cancer as an important potential risk.
4	30-Nov-2015	Addition of two new important identified risks (congenital malformations and co-administration of letrozole with tamoxifen). Completion of additional PV activity (FACE Study)	Congenital malformations and co-administration of letrozole with tamoxifen are already implemented in the SmPC. Due to off-label use in infertility treatment as well as guidelines recommending switch of aromatase inhibitor to tamoxifen (NCCN guidelines version 2.2015 – invasive breast cancer) with potential risk of overlap, it is agreed to implement both risks as important identified risks.
5	18-Jul-2016	Completion of additional PV activity (Study CFEM345MA17E1)	Main conclusions of Study CFEM345MA17E1 were added.