EU RMP	
Drug Substance	Fulvestrant
Version Number	13
Succession Number	1
Data lock point	30 September 2020
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for FASLODEX™ (fulvestrant)

The content of this RMP has been reviewed and approved by the deputy QPPV as delegated by EU QPPV. The electronic signature is available at the end of the document

Administrative Information

Rationale for submitting an updated RMP:

Safety concerns have been reassessed in line with Good Pharmacovigilance Practices (GVP) Module V Revision 2 and also in accordance with the Pharmacovigilance Risk Assessment Committee (PRAC) recommendations (Procedure number: EMEA/H/C/PSUSA/00001489/202004) on the European Union (EU) Periodic Benefit Risk Evaluation Report (PBRER): 26 April 2017 to 25 April 2020.

Summary of significant changes in this RMP:

The EU RMP has been transferred to EU RMP template Rev 2.0.1 accompanying Good Pharmacovigilance Practices (GVP) Module V-Risk management systems (Revision 2), and Safety concerns have been reassessed and removed.

Updates other than those related to the revised template are summarized below:

Part II SVII

Removal of the following safety concerns previously classified as an important identified risk:

Injection site reaction

Increased risk of bleeding at the injection site

Hypersensitivity reactions

Hepatobiliary disorders

Venous thromboembolic events

Removal of the following safety concerns previously classified as an important potential risk:

Reduced bone mineral density (osteopenia) and osteoporosis

Ischaemic cardiovascular events

Endometrial dysplasia

Interstitial lung disease

Vasculitis

Pulmonary micro-embolism of oily solutions

Reprotoxicity (fertility, pregnancy and lactation)

Removal of the following safety concerns previously classified as missing information:

Paediatric use

Use in patients with hepatic impairment

Use in patients with severe renal impairment

Part II SVIII

Amended in accordance with removal of all the safety concerns for FASLODEX.

Part V

Amended in accordance with removal of all the safety concerns for FASLODEX.

Part VI

Amended in accordance with removal of all the safety concerns for FASLODEX.

Other RMP versions under evaluation	Not applicable
Details of currently approved RMP	**Version Number**: 12 **Approved with procedure**: EMEA/H/C/000540/II/0059 **Date of approval:** 09 November 2017

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AI	Aromatase Inhibitors
AUC	Area Under Curve
BMD	Bone Mineral Density
CaCom database	Cancer and Co-morbidity database
CDS	Core Data Sheet
CI	Confidence Interval
CID	Commercialisation Investment Decision
Cmax	Concentration maximum
CNS	Central Nervous System
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EEA	European Economic Area
ER	Estrogen Receptor
ET	Estrogen Therapy
EU	European Union
HER 2	Human Epidermal Growth Factor receptor 2
HR	Hazard Ratio
HR+	Hormone Receptor positive
ILD	Interstitial Lung Disease
LHRH	Luteinizing Hormone-Releasing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
PBRER	Periodic Benefit Risk Evaluation Report
PgR+	Progesterone Receptor positive
PI	Prescribing Information
PK	Pharmacokinetics
PPP	Progressive Precocious Puberty
PR	Progesterone Receptor
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
RCT	Randomised Controlled Trial
RMM	Risk Minimisation Measure

Abbreviation/ Special term	Definition/Explanation
RMP	Risk Management Plan
SEER	Surveillance Epidemiology and End Results
SmPC	Summary of Product Characteristics (EU)
UK	United Kingdom
US	United States
VTE	Venous Thromboembolic Events

I. PART I: PRODUCT OVERVIEW

Table I Product Overview

Active substance(s) (INN or common name)	Fulvestrant
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic antiestrogen (ATC code: LO2BA03)
Marketing Authorisation Holder	AstraZeneca
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	FASLODEX
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: antiestrogen
	Summary of mode of action: FASLODEX is an anti-oestrogen that has a novel mode of action leading to down-regulation of oestrogen receptor (ER) protein and can be described as an ER down-regulator. FASLODEX completely blocks the trophic actions of oestrogens without itself having any partial agonist oestrogen-like activity. FASLODEX binds to ERs in a competitive manner with a high affinity comparable to that of oestradiol.
	Important information about its composition: Not applicable

Table I Product Overview

Hyperlink to the Product Information	FASLODEX , Summary of Product Characteristics
Indication(s)	Current Faslodex is indicated: ▪ as monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women: - not previously treated with endocrine therapy, or - with disease relapse on or after adjuvant antiestrogen therapy, or disease progression on antiestrogen therapy. ▪ in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy. In pre-or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.
	Proposed : Not applicable
Dosage	Current 500 mg administered intramuscularly as two 5 mL injections (250 mg/5 ml), at intervals of 1 month with an additional 500 mg dose given 2 weeks after the initial dose
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection, 250 mg/5 mL, clear, colourless to yellow, viscous liquid.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Epidemiological information is not commonly available for the specific target population for hormone receptor [HR]-positive or human epidermal growth factor receptor 2 [HER-2]-negative breast cancer. Therefore, epidemiological data in this document are mostly presented for the breast cancer population overall.

II.1.1 Breast Cancer

Incidence

Breast cancer is by far the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all female cancers) (Globocan 2012). Incidence rates vary from 27 per 100,000 women in Middle Africa and Eastern Asia to 96 per 100,000 women in Western Europe, and are high (greater than 80 per 100,000) in developed regions of the world (except Japan) and low (less than 40 per 100,000) in most of the developing regions.

No studies have been identified that reported incidence rates for hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. However, several population-based studies were identified that evaluated the proportion of all incident invasive breast cancers that were hormone receptor-positive, HER2-negative, including advanced stage (at diagnosis) hormone receptor-positive, HER2-negative breast cancer (Blows et al 2010, Kurian et al 2010, Parise et al 2009, Puig-Vives et al 2013, Spitale et al 2009, Yang et al 2007). Using information from these studies to calculate pooled averages, an estimated 65.7% of all incident breast cancers (all stages) are hormone receptor-positive, HER2-negative, and an estimated 9.3% of all incident breast cancers are advanced stage hormone receptor-positive, HER2-negative. Based on these data, in the European Union (EU), from 15.6% to 17.4% of all incident breast cancers are advanced hormone receptor-positive, HER2-negative (Puig-Vives et al 2013, Spitale et al 2009) and in the United States (US), an estimated 8.8% of all incident breast cancers are advanced stage hormone receptor-positive, HER2-negative (Parise et al 2009). Although the rates from these studies did not identify the proportion of pre- and perimenopausal women, the proportion of postmenopausal women ranged from approximately two-thirds to threequarters.

New or incident cases of locally advanced or metastatic breast cancer will be detected at diagnosis and, for earlier-staged disease, for a subpopulation who later progress. At diagnosis, less than 5% of breast cancer patients are diagnosed with Stage IV disease, most with HR+ disease.

In a registry based study, in 2 countries reporting relevant data (Norway and Germany), approximately 5% of patients with HR-positive breast cancer (1,742/39,276) had early breast cancer that had progressed to locally advanced or metastatic breast cancer, and had received no prior endocrine therapy (Bastiaannet et al 2016).

Prevalence:

On 01 January 2010, in the US there were approximately 2.8 million women alive who had a history of cancer of the breast (Howlader et al 2013). It is estimated that 5-year prevalence of female breast cancer in the world is approximately 5.2 million and 1 million in Northern America and 1.8 million in Europe (Bray et al 2013).

Demographics of the population in the authorised indication and risk factors for the disease:

Risk for breast cancer increases with age, with the peak incidence rate among women aged 75-79, and virtually no cases among women under 15 based on US Surveillance Epidemiology and End Results Program (SEER) data (Howlader et al 2013). There are large variations (5-fold) in occurrence of breast cancer and survival between different countries and regions (Bray et al 2013). Many factors underlie these variations (i.e. age, ethnicity, socio-economic status, mammography use, and access to high-quality care) (Key et al 2001).

From the National Cancer Institute's SEER program, 251,147 women between 20 and 79 years who were diagnosed with invasive breast cancer between 1992 and 2008 were analyzed for hormone status and baseline characteristics. Compared to ER+/PgR+ patients, the ER-/PgR- and ER-/PgR+ patients were somewhat more likely to be less than 50 at diagnosis (27.5% versus 36.9% and 43.7%), non-white (17.3% versus 25.3% and 22.8%) and to present with Stage II-IV diseases (48.1% versus 64.6% and 58.7%). Compared to ER+/PgR+, the ER+/PgR- patients were somewhat more likely to be older than 50 (72.5% versus 80.3%), Black (6.8% versus 9.1%) and to present with Stage III–IV cancers (15.3% versus 20.2%) (Chen et al 2014).

The main existing treatment options:

In postmenopausal women, with hormone receptor positive locally advanced or metastatic breast cancer, with no identifiable biomarkers, the preferred treatment is endocrine therapy (ET) in the majority of cases, excluding only those with visceral crisis or multiple lines of endocrine resistance (Cardoso et al 2018). Treatment options in ET, include non-steroidal Aromatase Inhibitors (AIs) such as anastrozole and letrozole, steroidal AIs such as exemestane, selective ER down regulator such as fulvestrant either alone or in combination with non-steroidal AI, selective estrogen receptor modulator such as tamoxifen and toremifene. In addition, the combination of everolimus with one of the endocrine agents,

described above, is also available. With the introduction of a new class of agents, the CDK4/6 inhibitors, resulting in significant prolongation of progression free survival, currently, there are 3 approved agents palbociclib, ribociclib and abemaciclib, that are available for use in combination either with non-steroidal AI or Fulvestrant (NCCN Guidelines 2020). The agents as described above for postmenopausal women can be used along with ovarian ablation or suppression in pre-menopausal women with hormone receptor positive advanced breast cancer. There are no definitive current recommendations for an optimal sequence of the endocrine treatment cascade (Cardoso et al 2018 and NCCN Guidelines 2020) as it depends on the choice of previously used therapies in the (neo)adjuvant or advanced settings, the burden of the disease, patients' preference and tolerance levels to treatment.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In the postmenopausal women with advanced breast cancer, whose disease had progressed after treatment with tamoxifen, in independent Randomised Controlled Trials (RCT), that evaluated anastrozole 1mg (Buzdar et al 1998), or letrozole 2.5 mg (Buzdar et al 2001), or exemestane (Kaufmann et al 2000), as second line treatment, majority of the patients (80 – 90%), had experienced disease progression by the end of the study and approximately 60% of the population had died by a median follow up duration of approx.30 months (Dombernowsky et al 1998; Buzdar et al 1998).

In postmenopausal women with advanced breast cancer and who were hormone receptor positive, the objective response rates with tamoxifen (as first line treatment) ranged between 21% - 31%, with disease progression observed in more than 80% of patients by 24 – 32 months and mortality rates observed were up to 65% by 46 months of follow up (Bonneterre et al 2001; Mouridsen et al 2003; Paridaens et al 2008). With AIs as a first line treatment in postmenopausal women with hormone receptor positive advanced breast cancer, disease progression occurred in at least 80% of patients within 36 months of treatment (Bonneterre et al 2001; Paridaens et al 2008; Mouridsen et al 2003) and mortality rates ranged from 55% - 65% with these agents (Nabholtz et al 2003; Paridaens et al 2008; Mouridsen et al 2003).

Despite so many treatment options, advanced breast cancer remains virtually an incurable disease with a median overall survival of 3 years and a 5-year survival ranging between 10% – 40% (Plichta et al 2018; Cardoso et al 2018).

Important co-morbidities:

The total number of co-morbidities increases with age (Yancik et al 2001). Scientific knowledge remains limited on patterns and prevalence of comorbidity at time of breast cancer diagnosis. Results based on medical record shows that high impact co-morbidity was present in more than 70% of breast cancer patients older than 80 years at diagnosis. The

corresponding estimate for patients aged 40-50 years was 6% (Houterman et al 2004). In a population-based study, the prevalence of co-morbidity increased from less than 9% in breast cancer patients aged <50 years to 56% for patients aged >80 years.

The most frequent conditions were cardiovascular disease (7%), diabetes mellitus (6%) and previous cancer (7%) (Louwman et al 2005). Some co-morbidity may be etiologically related to the tumour while others are age related and chronic, but not necessarily disabling. The Cancer and Co-morbidity database (CaCom Database) is a compilation of Swedish national health registries and contains all cases of cancer registered in the Swedish National Cancer Register between 1992 and 2006, and in addition there is information on any prior cancers reported in these same individuals in the period from 1958-1991. These data were then matched with the nationwide Swedish Hospital Discharge Register to obtain all in-patient discharge data for all hospitalizations in these individuals occurring from 1987 up to 2006. These data were utilised to systematically assess the frequency of subsequent co-morbidities in the breast cancer patients.

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from non-clinical data

Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Injection of the approved formulation of FASLODEX caused muscle damage in the form of myositis, necrosis, fibrosis (dog only) and granulomata in the dog and rabbit, and fibrous cyst with associated inflammation in the rat. There were no major differences between reactions caused by FASLODEX injections and the vehicle suggesting that the muscle damage was caused by the vehicle and not by FASLODEX itself. In rats, the local irritant effects at the intramuscular injection sites were attributable to the formulation ingredients and not FASLODEX.

This is considered not to be a safety concern as injection site reaction is adequately characterised in labels and well understood and managed in clinical practice.

Reproductive/developmental toxicity

FASLODEX showed effects upon reproduction and embryo/foetal development consistent with its antiestrogenic activity, at doses similar to the clinical dose. In rats, FASLODEX caused a reversible reduction in female fertility and embryonic survival, dystocia, and an increased incidence of foetal abnormalities, including tarsal flexure. In rabbits dosing of FASLODEX resulted in a failure to maintain pregnancy and increases in placental weight and post-implantation loss, but there were no effects on foetal development. Additionally, it was shown that FASLODEX was present in rat milk at levels significantly higher than those in rat plasma.

The risk of reproductive toxicity in patients treated with FASLODEX has not been studied in clinical trials. Patients of childbearing potential are advised to use effective contraception during treatment with FASLODEX and for 2 years after the last dose. FASLODEX is contraindicated in pregnant women.

This risk is adequately characterized in labels and is monitored through routine pharmacovigilance activities

Genotoxicity

No key findings identified.

Carcinogenicity

A two-year rat oncogenicity study (intramuscular administration) showed an increased incidence of ovarian benign granulosa cell tumours in females at the high dose. In a two-year mouse oncogenicity study, oral dosing was associated with an increased incidence of sex cord stromal tumours (both benign and malignant) in the ovary. The neoplastic findings in mice were confined to female animals and occurred at exposures of $\geq$ 8 times the clinical exposure at the 500 mg dose, based on area under the curve (AUC). Induction of such tumours is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by antiestrogen in cycling animals. Therefore, these findings are not considered to be relevant to use of FASLODEX in postmenopausal women with advanced breast cancer or pre-and perimenopausal women receiving an LHRH agonist.

Safety pharmacology

Cardiovascular system, including potential effect on the QT interval

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen, but these occurred in animals exposed to far higher levels of FASLODEX than those recorded in patients (C_{max} >15 times) and are, therefore, considered to be of no significance for human safety at the clinical dose.

Nervous system

No key findings identified

Respiratory System

No key findings identified.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Estimates of overall cumulative exposure is provided based on actual exposure data from the following completed clinical trials as of 30 September 2020:

FMAS, EFECT, FINDER I, FINDER II, CONFIRM, CHINA CONFIRM, FIRST, IL0020, IL0021, IL0025, IL0041, IL0050, ABCSG21, IL0063, NEWEST, D6997L0018, 9238GRC/0002, IL0069, D699BC00001 (FALCON) and D6998L00004 (FLOWER).

Exposure data includes all doses of FASLODEX including 250mg and 500mg.

This is not a comprehensive list of all studies in the FASLODEX clinical development programme as some clinical trials were carried out in 1990s and 2000s. Legacy systems and documents containing this information are no longer available.

The Estimated cumulative subject exposure from clinical trials for FASLODEX is 3569 subjects.

Table II.2 Estimated cumulative subject exposure from clinical trials

Dose	Number of subjects
250 mg	1898
500 mg	1270
Others[a]	401
Total	3569

[a]150mg, 300mg, 600mg, and 750mg of high strength formula

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table II.3 and Table II.4, respectively.

Table II.3 Estimated cumulative subject exposure to FASLODEX from completed clinical trials by age and sex

	Number of subjects*				
Age range (years)	**Female 250 mg**	**Female 500 mg**	**Female – other doses**	**Male 500 mg**	**Total**
<18	-	-	30	-	30
18-65	1112	776	212	30	2130
66-75	492	343	94	-	929
>75	269	91	35	-	395
Total	1873	1210	371	30	3484

*Available Data from completed clinical trials as of 30 September 2020.

Table II.4 Estimated cumulative subject exposure to FASLODEX from completed clinical trials by racial group

Racial group	Number of subjects*			
	Fulvestrant 250 mg	**Fulvestrant 500 mg**	**Fulvestrant other[a]**	**Number of subjects**
Caucasian	802	581	179	1562
White	675	175	151	1001
Oriental	164	158	51	373
Other	100	37	6	143
Black	40	14	7	61
Hispanic	14	0	5	19
Unknown	16	31	2	49
Japanese	4	0	0	4
Asian	3	269	0	272
Total	1818	1265	401	3484

*Available data from completed clinical trials as of 30 September 2020.

[a]150mg, 300mg, 600mg, 750mg of High strength formula

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Hypersensitivity to the active substance or to any of the excipients

Reason for exclusion:

Patients with known severe hypersensitivity to FASLODEX or any of the excipients of this product were excluded from the clinical trials because of increased predisposition to develop AEs related to hypersensitivity reactions and might have confounded a complete understanding of the safety and efficacy data of FASLODEX thereby affecting the interpretability of data.

Is it considered to be included as missing information: No

Rationale:

In Section 4.3 of the FASLODEX Summary of Product Characteristics (SmPC), in patients with known hypersensitivity to the drug substance or any of the excipients are contraindicated, therefore this population is not considered to be relevant for inclusion as missing information.

Pregnancy and lactation

Reason for exclusion:

As expected with a potent antiestrogen, studies in animals with FASLODEX have shown reproductive toxicity. FASLODEX is found in rat milk at levels significantly higher than those in rat plasma. Hence pregnant and breast-feeding women were excluded to ensure the general safety of the foetus and child.

Is it considered to be included as missing information: No

Rationale:

Section 4.3 (Contraindications) of the SmPC lists pregnancy and lactation as contraindications for FASLODEX treatment. Section 4.6 (Pregnancy and lactation) of the SmPC also advises to avoid FASLODEX in pregnant or lactating women and to use effective contraception during treatment with FASLODEX and for 2 years after the last dose in patients of childbearing potential. Therefore, exposure in this population is expected to be very limited and is not relevant for including as a missing information

Presence of life-threatening metastatic visceral disease defined as extensive hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread

Reason for exclusion:

This represents a general exclusion criterion to ensure that patients were able to be on study long enough so as not to confound efficacy or safety findings in studies.

Is it considered to be included as missing information: No

Rationale:

There is no evidence to suspect the safety profile of this population may differ to that characterised so far for the general targeted population.

More than one prior regimen of chemotherapy and / or endocrine therapy for advanced disease

Reason for exclusion:

This represents a general exclusion criterion to ensure homogeneity of study patients.

Is it considered to be included as missing information: No

Rationale:

There is no evidence to suggest that use of more than one regimen of chemotherapy and/or endocrine therapy result in a specific safety concern, or a different safety profile to that of the general target population, therefore this population is not relevant for consideration as missing information.

Extensive radiation therapy within the last 4 weeks (greater than or equal to 30% marrow or whole pelvis or spine) or cytotoxic treatment within the past 4 weeks prior to screening laboratory assessment or strontium-90 (or other radiopharmaceuticals) within the past 3 months

Reason for exclusion:

To minimise the risk of overlapping toxicity and risk of being a confounding factor in assessing the efficacy of FASLODEX in studies.

Is it considered to be included as missing information: No

Rationale:

This exclusion criterion allows for a meaningful data interpretation, and there is no evidence to suggest that use of radiation therapy or cytotoxic treatment options within the timeframes stated result in a specific safety concern, or a different safety profile to that of general target population, therefore this population is not relevant for consideration as missing information.

Treatment with a non-approved intervention within 4 weeks before randomisation

Reason for exclusion:

To minimise the risk of overlapping toxicity and risk of being a confounding factor in assessing the efficacy of FASLODEX in studies.

Is it considered to be included as missing information: No

Rationale:

This exclusion criterion allows for a meaningful data interpretation, and there is no evidence to suggest that use of other interventions such as radiation therapy or cytotoxic treatment options within the timeframes stated result in a specific safety concern, or a different safety profile to that of general target population, therefore this population is not relevant for consideration as missing information.

Current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix)

Reason for exclusion:

This represents a general exclusion criterion to ensure homogeneity of study patients and also to minimise the risk of overlapping toxicity and risk of being a confounding factor in assessing the efficacy of FASLODEX in studies.

Is it considered to be included as missing information: No

Rationale:

There is no evidence to suspect that the safety profile of this population is different to that characterised so far for the general targeted population.

Any of the following laboratory values: Total bilirubin> 1.5 X ULRR, ALT or AST>2.5 ULRR if no demonstrable liver metastases or >5 ULRR in presence of liver metastases

Reason for exclusion:

Patients with elevated bilirubin and liver enzymes were excluded from clinical trials to protect the safety of subjects who participate in clinical trials.

Is it considered to be included as missing information: No

Rationale: There is the potential for this population to be at a greater risk of hepatic events however elevated bilirubin and elevated liver enzymes (ALT, AST, ALP, GGT) are listed in Section 4.8 "Undesirable effects" of FASLODEX SmPC with additional caution in Section 4.4 of SmPC "Special warnings and special precautions for use". Also use in patient with severe hepatic impairment (Child-Pugh category C) is a contraindication in Section 4.3 of SmPC and thus is not anticipated. Therefore the potential risk to this population is adequately managed through labelling and further characterisation is therefore not warranted.

History of bleeding diathesis DIC, clotting factor deficiency), or long term anticoagulant therapy (other than antiplatelet therapy and low dose warfarin) and Platelet<100X109/L

Reason for exclusion:

This exclusion was applied to reduce the potential risk of severe bleeding following intramuscular injection of FASLODEX.

Is it considered to be included as missing information: No

Rationale:

Use in patients with bleeding diathesis, thrombocytopenia and on anticoagulant therapy is not anticipated as use of FASLODEX in this population is cautioned in SmPC section 4.4 "Special warnings and special precautions for use" and therefore is not relevant for consideration as missing information.

II.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table II-5 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breast-feeding women	Not included in the clinical development program
Patient with relevant comorbidities: Patients with hepatic impairment	Exposure data for this population are not available
Patients with renal impairment	Exposure data for this population are not available
Patients with cardiovascular impairment (Any severe concomitant condition which makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the study protocol, eg, uncontrolled cardiac disease)	Not included in the clinical development program
Immunocompromised patients	Exposure data for this population are not available
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Patients with relevant different ethnic origin	Please refer to Table II-4 of Section 2 Module III: Clinical Trial Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on FASLODEX 's monthly actual ex-factory sales volume from each local affiliate. These data represent all FASLODEX formulation delivered to various distribution channels (e.g., wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of packs sold and the number of individual injections sold. FASLODEX is available as a 250 mg injection, with an approved dose of either 1 injection monthly (250 mg) or 2 injections monthly (500 mg). The exposure to FASLODEX in the marketed setting is calculated from the worldwide sales of the drug as follows:

250 mg Dose:

1 injection sold = 1 patient-month of treatment

12 injections sold = 1 patient year

X injections sold = (X/12) patient years

500 mg Dose:

2 injections sold = 1 patient-month of treatment

24 injections sold = 1 patient year

X injections sold = (X/24) patient years

More detailed patient-level data (e.g., Gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II.5.2 Exposure

Cumulative global post-marketing patient exposure for FASLODEX (250 mg and 500 mg) since launch to 30 September 2020 has been estimated to be approximately 450083 patient years (250 mg monthly dose) and 550872 patient years (500 mg monthly dose).

Exposure is summarised by dose and region in the table below.

Data stratified by indication, gender, age group, are not available.

Table II-10 Exposure by dose – Cumulative to 30 September 2020	
Dose	**Exposure (patient years)**
250 mg	450083
500 mg	550872

Patient years presented in the table are estimated figures based on sales data.

Table II-11 Exposure by country – Cumulative to 30 September 2020 (500 mg)		
Indication	**500 mg Exposure (patient years)**	**250 mg Exposure (patient years)**
European Union	183396	301839
North America	187014	86523
Japan	[redacted]	
International	113091	61720

Patient years presented in the table are estimated figures based on sales data.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The pharmacological activity of FASLODEX is such that it is highly unlikely that the drug would be misused or otherwise used for illegal purposes. There is no evidence to date after 450083 (250 mg monthly dose) and 550872 (500 mg monthly dose) patient years of post-marketing exposure since approval that FASLODEX has been subject to misuse or otherwise used for illegal purposes.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

II.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

II.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

Injection site reactions

Injection site reactions previously classified as an important identified risk is removed from the list of safety concerns.

'Injection site reactions' is well recognised and is an inherent risk associated with any intramuscular injection. However there could be also be a contributory role from patient factors and administration related factors. Over the 18 years of post-marketed use and with a cumulative exposure of over 450083 (250 mg) and 550872 (500 mg) patient years, until 30 September 2020, there have been 2669 case reports (with 3770 Adverse Events [AEs]) of injection site reactions of which 247 AEs were serious. Considering the case reports where the AE outcome was reported, 672 AEs were recovered, 338 AEs were recovering, 575 AEs had not recovered and one AE had a fatal outcome with limited information for complete assessment. The most frequently reported AEs were injection site pain (1132), injection site induration (364) and injection site erythema (204). Over the years, frequency and severity of injection site reactions remained stable. This risk is well understood and characterised with adequate warnings detailed in the SmPC under sections: 4.2 (Posology and method of administration), 4.4: (Special warnings and precautions for use), 4.8 (Undesirable effects, very common) and 6.6 (Special precautions for disposal and other handling).

In summary injection site reactions is a well-recognised risk, is adequately characterised and well understood and managed through the CDS and routine clinical practice. This risk does not warrant further characterisation in the pharmacovigilance plan or additional risk minimisation measures and does not impact the benefit risk profile of FASLODEX.

Increased risk of bleeding at the injection site

Increased risk of bleeding at the injection site previously classified as an important identified risk is removed from the list of safety concerns.

Bleeding at the injection site is an inherent risk associated with intramuscular injections. However there could be a predisposing role of patient factors (impaired coagulation) and administration factors. Cumulatively until 30 September 2020, 57 case reports (with 57 AEs) of injection site bleeding were reported of which 9 AEs were serious. The most commonly reported AE was injection site haematoma (55). Over the years, frequency and severity of bleeding at injection site remained stable.

Bleeding at injection site is a well-recognised risk for intramuscular injections. The risk is well managed through routine clinical practice and adequate warnings and instructions in the labels (SmPC section 4.4 Special warnings and precautions for use and section 6.6 Special precautions for disposal and other handling), as evidenced by the low number of reported events. This risk does not warrant further characterisation in the pharmacovigilance plan or additional risk minimisation measures. Increased risk of bleeding at the injection site does therefore not impact the benefit risk profile of FASLODEX.

Hypersensitivity reactions

Hypersensitivity reactions previously classified as an important identified risk is removed from the list of safety concerns.

Hypersensitivity is a common risk found with many drugs, it is largely idiosyncratic and difficult to mitigate. Cumulatively until 30 September 2020, 615 case reports (with 671 AEs) of hypersensitivity reactions were reported till 30 Sep 2020, of which 137 AEs were serious. Where the AE outcome was reported, 268 AEs were recovered/recovering and 81 AEs had not recovered. The most frequently reported events were Pruritus (260), Hypersensitivity (135) and Urticaria (114). Over the years, frequency and severity of hypersensitivity reactions remained stable. This risk is well understood and there are appropriate warnings in SmPC Section 4.3 (Contraindications) and Section 4.8 (undesirable effects) where the frequency of hypersensitivity reactions is listed as very common.

Hypersensitivity is a well-recognised risk for many injectables and is well managed through routine clinical practice and labelling. Therefore this risk does not warrant further characterisation in the pharmacovigilance plan or additional risk minimisation measures and does not impact the benefit risk profile of FASLODEX.

Hepatobiliary disorders

Hepatobiliary disorders (including hepatic failure and hepatitis) previously classified as an important identified risk is removed from the list of safety concerns.

Hepatobiliary disorders are widely recognized to occur with use of endocrine/hormonal therapy. With a cumulative exposure through 30 September 2020, of over 450083 (250 mg)

and 550872 (500 mg) patient years until 30 September 2020, there were 687 case reports with 881 AEs, of which 472 AEs were serious. Where the AE outcome was reported, 211 AEs recovered/recovering, 150 AEs not recovered, 86 AEs had fatal outcome. Upon review of cases with hepatobiliary disorders related fatal outcome, majority of the cases had either alternative causes, known risk factors, underlying disease or there was insufficient information to perform a complete assessment. The most commonly reported events were Alanine aminotransferase increased (85), hepatic function abnormal (84), Ascites (77), Aspartate aminotransferase increased (76), Hepatic enzyme increased (75), hepatic failure (48), hepatitis (15), acute hepatic failure (13). Over the years, frequency and severity of hepatobiliary disorders reactions remained stable.

Hepatobiliary disorders are well-recognized effects of FASLODEX and other endocrine treatments and as such their management is fully integrated into oncology clinical practice. This risk is also described in CDS Section 4.8 (undesirable effects). The majority of the reported events are laboratory abnormalities with no clinical outcome demonstrating that this risk is well managed. Although fatalities have been reported, in the majority of cases contributing factors are present. The topic has been an important identified risk and monitored through routine pharmacovigilance activities for 9 years without the emergence of any new safety signal. This risk does therefore not impact the benefit risk profile of FASLODEX and does not warrant further characterization in the pharmacovigilance plan or additional risk minimization measures.

Venous thromboembolic events

Venous thromboembolic events (VTE) previously classified as important identified risk is removed from the list of safety concerns.

Cumulatively until 30 September 2020, there have been 325 case reports with 348 AEs of VTE, 326 of which were serious. The most common AE is pulmonary embolism (149). Where the outcome was reported, 158 AEs were recovered/recovering, 47 were not recovered and 31 (8.9%) were fatal. The fatal AEs were associated with underlying disease or had limited information for a full assessment. Over the years, frequency and severity of VTE has remained stable with no new signal emerging. Considering the cumulative exposure for FASLODEX is over 450083 (250 mg) and 550872 (500 mg) patient years, and there is an inherent risk of VTE in this population, the number of reported cases is low.

Venous thromboembolism can be a severe condition with the potential for fatal outcomes, however in the field of oncology, and in particular breast cancer, it is well understood, and the management is fully integrated in to oncology clinical practice. In addition the FASLODEX SmPC provides adequate guidance in sections 4.4 (Special warnings and precautions for use) and 4.8 (undesirable effect). This important identified risk is therefore well managed through oncology clinical practice and labelling and does not impact benefit risk profile of

FASLODEX or warrant further characterisation in the pharmacovigilance plan or additional risk minimisation measures.

Reduced bone mineral density (osteopenia) and osteoporosis

Reduced bone mineral density (osteopenia) and osteoporosis previously classified as important potential risk is removed from the list of safety concerns.

Based on the antiestrogenic action, there is a theoretical possibility that bone mineral density (BMD) may be reduced by FASLODEX, however preclinical and clinical data do not support this theory. The results of NEWEST study showed that neoadjuvant treatment for up to 16 weeks in breast cancer patients with either FASLODEX 500 mg or 250 mg did not result in clinically significant changes in serum bone-turnover markers. This is supported by clinical data from Study 9238IL/0019 which investigated bone resorption in patients receiving FASLODEX by assessing the excretion of bone resorption markers (N-telopeptides and free deoxypyridinoline) which observed no reduction in BMD with FASLODEX treatment. In the pooled analysis of studies comparing FASLODEX 500 mg with FASLODEX 250 mg (CONFIRM, FINDER1, FINDER2, NEWEST), there were no events of reduced bone mineral density or osteopenia. In FALCON study, events suggestive of reduced bone density (osteopenia and osteoporosis) were low in both treatment arms (FASLODEX arm 500 mg-2.2% (5/228) and Arimidex arm 2.6% [6/232]). Cumulatively through 30 September 2020, there have been 327 case reports with 358 AEs of reduced bone mineral density (osteopenia) and osteoporosis. Where the outcome was reported, 145 AEs recovered/recovering and 58 AEs not recovered. The most commonly reported events were Femur fracture (55), Hip fracture (33), Pathologic fracture (33), osteoporosis (21), fracture (20) and femoral neck fracture (19).

This risk of reduced bone mineral density (osteopenia) and osteoporosis has been monitored as an important potential risk for 14 years. Given the stable frequency, absence of a new signal, underlying predisposition and continued lack of evidence of a causal association, this risk does not impact the benefit risk balance of FASLODEX and does not warrant additional pharmacovigilance activities or specific clinical risk minimisation measures.

Ischaemic cardiovascular events

Ischaemic cardiovascular events previously classified as an important potential risk is removed from the list of safety concerns.

There is no recognised mechanism of action for this risk with FASLODEX. In a pooled analysis of studies comparing FASLODEX 500 mg with FASLODEX 250 mg (CONFIRM, FINDER1, FINDER2, NEWEST), the frequency of ischaemic cardiovascular events in 500 mg arm was 0.9% (5/560 patients) and in 250 mg arm was 0.7% (4/567 patients). In the

FALCON study the frequency of ischaemic cardiovascular disease in 500 mg arm was 1.3% (3/228). Cumulatively through 30 September 2020, there have been 89 case reports (with 95 AEs) of ischaemic cardiovascular events in the AZ Global safety database and the most commonly reported event was Myocardial infarction (31 case reports). Of the 95 AEs, 77 events were serious. Where the outcome was reported, 41 AEs were recovered/recovering, 8 AEs not recovered, and 12 AEs had a fatal outcome with the cause of death reported as myocardial ischaemia, acute myocardial infarction, coronary artery disease, cardiac failure congestive, metastasis to peritoneum, and breast cancer metastatic. A review of these cases does not indicate a causal association with FASLODEX. All the case reports included known risk factors or there was insufficient information to perform a complete assessment.

Ischaemic cardiovascular events have the potential to have serious clinical consequences. However this risk has been closely monitored as an important potential risk since 2006 and there have been no new signals. Given the lack of mode of action, the relatively low number of cases and the continued lack of evidence of a causal association, ischaemic cardiovascular events do not impact the benefit-risk profile of FASLODEX. There are no additional pharmacovigilance activities or specific clinical measures in place.

Endometrial dysplasia

Endometrial dysplasia previously classified as an important potential risk is removed from the list of safety concerns.

This topic was considered as an important potential risk based on the observed effects of selective ER modulators on the endometrium. However, FASLODEX is a pure anti-oestrogen and as such does not have a stimulatory effect on the endometrium. This is supported by clinical data where no cases of endometrial dysplasia were reported. Cumulatively until 30 September 2020, there have been 15 case reports (with 15 AEs) of endometrial dysplasia with 11 serious AEs with no fatal outcome. Where the outcome was reported, 7 AEs were recovered and the most commonly reported event is endometrial cancer(6).

Endometrial dysplasia has been monitored as an important potential risk for 14 years. Given the low number of cases in this population despite having an underlying predisposition and possible previous use of other endocrine therapies and the continued lack of evidence of a causal association, endometrial dysplasia does not impact the benefit-risk profile of FASLODEX. No specific clinical measures and additional pharmacovigilance activities are warranted.

Interstitial Lung disease

Interstitial lung disease previously classified as an important potential risk is removed from the list of safety concerns.

In the pooled analysis of studies comparing FASLODEX 500 mg with 250 mg (CONFIRM, FINDER1, FINDER2, NEWEST) the frequency of interstitial lung disease in 500 mg arm was 0.2% (1/560 patients) and no case reports were reported in 250 mg arm. Cumulatively until 30 September 2020, there have been 124 case reports (with 127 AEs) of ILD with 111 serious AEs. The most frequent events reported were interstitial lung disease (49) and pneumonitis (42). Where the outcome was reported, 52 AEs were recovered/recovering, 14 AEs not recovered and 16 had a fatal outcome. The majority of the fatalities were associated with underlying disease or there was limited information for assessment.

Interstitial lung disease has been closely monitored as an important potential risk since 2009. Given the low frequency and lack of evidence of causality, this risk does not impact the benefit risk balance of FASLODEX and additional pharmacovigilance activities or specific clinical measures are not warranted.

Vasculitis

Vasculitis previously classified as an important potential risk is removed from the list of safety concerns.

Non-clinical data in dogs showed reports of vasculitis which was considered unrelated to treatment. Also, this finding has not been confirmed in clinical studies where there have been no reports of vasculitis. Cumulatively through 30 September 2020, there have been 10 case reports (with 11 AEs) of vasculitis in AZ Global safety database. Of the 11 AEs, 10 events were serious with no fatal outcome. For the 3 reports where outcome was provided 3 recovered and 2 did not recover.

Vasculitis has been monitored as an important potential risk since 2011. Given the very low number of cases and the continued lack of evidence of a causal association, vasculitis does not impact the benefit-risk profile of FASLODEX and further characterisation in the pharmacovigilance plan is not warranted.

Pulmonary micro embolism of oily solutions

Pulmonary micro embolism of oily solutions previously classified as an important potential risk is removed from the list of safety concerns.

It has been reported that lymphogenic absorption of oil from oily injections may give rise to pulmonary microembolisation (Svendsen et al 1980). However, there have been no reports of pulmonary micro embolism with FASLODEX treatment in clinical trials or post market use.

This risk does not therefore impact the benefit risk balance of FASLODEX and further characterisation in the pharmacovigilance plan is not warranted.

Reprotoxicity (fertility, pregnancy and lactation)

Reprotoxicity previously classified as an important potential risk is removed from the list of safety concerns.

In the pooled analysis of studies comparing FASLODEX 500 mg with FASLODEX 250 (CONFIRM, FINDER1, FINDER2, NEWEST) and FALCON study there were no reports of reprotoxicity (fertility, pregnancy and lactation) since these studies included only post menopausal women. Cumulatively until 30 September 2020, there have been 9 cases of exposure during pregnancy with no adverse pregnancy outcomes and there were no reports of exposure during breast feeding. The SmPC provides relevant information in sections 4.3 (Contraindications), 4.6 (Fertility, Pregnancy and Lactation) and 5.3 (Preclinical safety data) and as a consequence exposure in this population is very low, as evidenced by the small number of case reports.

Given the presence of adequate warnings in the labels, exposure in this population is very low as evidenced by small number of case reports. Considering this together with continued lack of evidence of a causal association, reprotoxicity does not impact the overall benefit-risk profile of FASLODEX. This risk is monitored through routine pharmacovigilance activities and additional pharmacovigilance activities and specific clinical measures are not warranted.

Paediatric use

Use in paediatric population (0 to <18 years) previously classified as missing information is removed from the list of safety concerns.

In a study (FMAS) performed to evaluate the safety, efficacy and PK of FASLODEX in girls (aged 1 to 8 years) with PPP (progressive precocious puberty) associated with McCune Albright syndrome, 29 girls completed the 12 month study treatment phase. Twenty girls were followed up for 5 years safety surveillance. The study revealed no new or significant safety findings. Cumulatively till 30 September 2020, there are 34 case reports in the AstraZeneca global safety database of use in paediatric patients (<18 years), 30 of which were serious. Most of these cases concerned use of FASLODEX in patients with PPP associated with McCune Albright syndrome (28 clinical trial cases, 4 spontaneous and 2 literature). The adverse events reported in these cases were consistent with other features of the underlying condition. Twenty one of these cases were recovered and 12 cases not recovered. Review of these cases did not indicate any new safety concerns.

The FASLODEX label (SmPC sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use) clearly states that use in children and adolescents is not recommended, usage in this population is therefore low and this is demonstrated by the low number of case reports received. Given the lack of evidence of a different safety profile in

paediatric population and the very low exposure this safety concern is not relevant for inclusion as missing information.

Use in severe hepatic impairment

Use in patients with severe hepatic impairment previously classified as missing information is removed from the list of safety concerns.

A review of the global safety database cumulatively until 30 September 2020, identified 353 case reports with medical history of hepatic impairment that included 1289 AEs, 627 of which were serious. There were 51 case reports with fatal outcome, the cause of death in 17 cases was disease progression and for the remaining case reports there was limited information for an assessment. The most commonly reported events were malignant neoplasm progression (34), neutropenia (26) and nausea (24). Although these cases did not report the grade of pre-existing hepatic impairment, review of these cases does not indicate any adverse event consistent with accumulation of FASLODEX and resulting toxicity. FASLODEX is metabolised primarily in the liver, hepatic impairment may therefore impede the clearance of FASLODEX which could in turn affect the safety profile. FASLODEX labels warns that FASLODEX should be used with caution in patients with hepatic impairment. The label also states no dose adjustment is required in patients with Child-Pugh category A and B hepatic impairment and cautions that use has not been evaluated in patients with Child-Pugh C hepatic impairment but that clearance may be reduced.

As use in patients with severe hepatic impairment (Child-Pugh category C) is not anticipated due to the contraindication and there is no evidence that the safety profile in this population is different to that of the general indicated population or Child-Pugh category A/B hepatic impairment, this topic is not relevant for consideration as missing information and additional pharmacovigilance activities are not warranted.

Use in severe renal impairment

Use in patients with severe renal impairment previously classified as missing information is removed from the list of safety concerns.

FASLODEX is rapidly cleared by the hepatobiliary route and renal elimination is negligible (less than 1%). A review of the global safety database cumulatively through 30 September 2020, identified 170 case reports with medical history of renal impairment containing 552 AEs, 299 of which were serious. There were 51 case reports with fatal outcome and cause of death in majority of cases is due to disease progression, or with limited information for an assessment. The most commonly reported events were nausea (17), arthralgia (14), malignant neoplasm progression (10), and injection site pain (10). Although these cases did not report

the grade of pre-existing renal impairment, review of these cases does not indicate any adverse event consistent with accumulation of FASLODEX and resulting toxicity.

FASLODEX SmPC sections 4.2 (Posology and method of administration, special population, Renal impairment) and 4.4 (Special warnings and precautions for use) caution when use in patients with severe renal impairment and specifies severe renal impairment patients were not evaluated in studies. Use in patients with severe renal impairment is anticipated to be low given the information provided in the SmPC and as there is no evidence of a different safety profile in this population it is not relevant for consideration as missing information and additional pharmacovigilance activities are not warranted.

II.7.3 Details of important identified risks, important potential risks and missing information

II.7.3.1 Presentation of important identified risks and important potential risks

None.

II.7.3.2 Presentation of missing information

None.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the safety concerns

There are no safety concerns for FASLODEX.

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concern(s):

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no ongoing or planned additional pharmacovigilance activities.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not Applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Not applicable

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR FASLODEX

This is a summary of the risk management plan (RMP) for FASLODEX. The RMP details important risks of FASLODEX and how more information will be obtained about FASLODEX' s risks and uncertainties (missing information).

FASLODEX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FASLODEX should be used.

This summary of the RMP for FASLODEX should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of FASLODEX' s RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

FASLODEX is authorised for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women of any age: Not previously treated with endocrine therapy or Previously treated with endocrine therapy (antiestrogen or aromatase inhibitor therapy), irrespective of whether their postmenopausal status occurred naturally or was artificially induced. FASLODEX in combination with Palbociclib is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy. (see PI for the full indication). It contains fulvestrant as the active substance and it is given as, 500 mg (two 250 mg/5 mL) solution for injection.

Further information about the evaluation of FASLODEX's benefits can be found in FASLODEX's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/faslodex.

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of FASLODEX, together with measures to minimise such risks and the proposed studies for learning more about FASLODEX's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC/PI addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

VI.2.1 List of important risks and missing information

Important risks of FASLODEX are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of FASLODEX. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

There are no important risks or missing information for FASLODEX.

VI.2.2 Summary of important risks

There are no important risk for FASLODEX.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies required for FASLODEX.

VI.2.3.2 Other studies in post-authorisation development plan

There are no studies required for FASLODEX.

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