9 November 2017
EMA/CHMP/810299/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fulvestrant Mylan

International non-proprietary name: fulvestrant

Procedure No. EMEA/H/C/004649/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

^{14}C	radioactive carbon (molecular weight = 14)
AE	anti-estrogen
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
CBR	clinical benefit rate
CEP	Certificate of Suitability of the Ph. Eur.
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum concentration
DoCB	duration of clinical benefit
EDQM	European Directorate for the Quality of Medicines
ER	oestrogen receptor
EU	European Union
EU	Endotoxin Unit
GC	Gas Chromatography
HPLC	High performance liquid chromatography
HR	hazard ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of
IH	In house
IM	intramuscular
IR	Infrared
LA	long-acting
MDI	Maximum daily intake
NF	National Formulary
NMT	Not more than
ORR	objective response rate
OS	overall survival

PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia
PL	package leaflet
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
RMP	Reference Medicinal Product
SA	short-acting
SC	subcutaneous
SD	Sprague-Dawley
SmPC	Summary of Product Characteristics
TLC	Thin layer chromatography
TTC	Threshold of toxicological concern
UK	United Kingdom
USP	United States Pharmacopoeia
V_{max}	maximum reaction velocity

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 25 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Fulvestrant Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Fulvestrant is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-estrogen therapy, or disease progression on therapy with an anti-estrogen.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Faslodex instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Faslodex, 250 mg, solution for injection
- Marketing authorisation holder: AstraZeneca UK Limited
- Date of authorisation: 10/03/2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/269/001-002

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Faslodex, 250 mg, solution for injection
- Marketing authorisation holder: AstraZeneca UK Limited
- Date of authorisation: 10/03/2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/269/001-002

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Natalja Karpova Co-Rapporteur: N/A

- The application was received by the EMA on 25 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 23 March 2017.
- During the meeting on 21 April 2017 the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 21 August 2017.
- During the PRAC meeting on 1 September 2017 the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 9 October 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 26 October 2017.
- During the meeting on 9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Fulvestrant Mylan.

2. Scientific discussion

2.1. Introduction

The Applicant Mylan S.A.S. submitted marketing authorization application for Fulvestrant Mylan 250 mg/5ml solution for injection. The application is referring to Article 10(1) of Directive 2001/83/EC, as amended.

The proposed product Fulvestrant Mylan 250 mg/5 ml solution for injection is long – acting intramuscular depot formulation containing Fulvestrant as active substance. Fulvestrant is a chemical substance and the dosage form has been developed as generic product to the centrally authorised product Faslodex containing the same active substance in the same pharmaceutical form. The reference product Faslodex 250 mg/5 ml Solution for Injection (Faslodex) authorised in EU via the centralised procedure by AstraZeneca UK Limited. Date of issue of marketing authorisation valid throughout the European Union for Faslodex is 10th March 2004, Marketing authorisation number EU/1/03/269/001, EU/1/03/269/002.

The claimed indications for this generic application are the same as those of reference product Faslodex:

Fulvestrant is indicated 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 anti-estrogen therapy, or disease progression on antiestrogen therapy.

The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.

Fulvestrant Mylan should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock.

Fulvestrant is a competitive estrogen receptor (ER) antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity. The mechanism of action is associated with down-regulation of estrogen receptor protein levels. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection in a pre-filled syringe containing 250 mg of fulvestrant as active substance.

Other ingredients are benzyl benzoate, benzyl alcohol, anhydrous ethanol and refined castor oil.

The product is available in a clear type 1 glass pre-filled syringe with polypropylene plunger rod, fitted with a tamper-evident closure, containing 5 ml Fulvestrant Mylan solution for injection. A safety needle (BD SafetyGlide) for connection to the barrel is also provided, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of fulvestrant is 7α-[9-(4,4,5,5,5-pentafluoropentylsulfinyl) nonyl]estra-1,3,5(10)triene-3,17β-diol corresponding to the molecular formula $C_{32}H_{47}F_5O_3S$. It has a relative molecular mass of 606.77 $gmol^{-1}$ and the following structure:

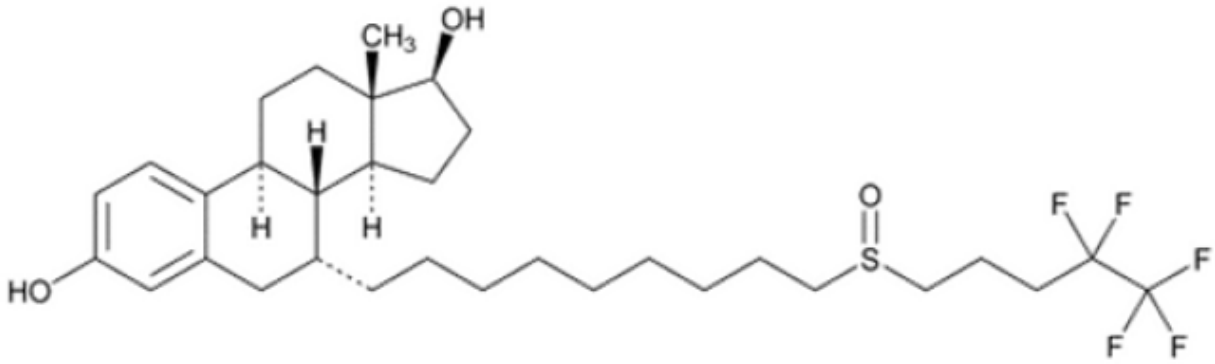

Figure 1: active substance structure

The active substance is a white or almost white non-hygroscopic powder. It shows very high lipophilicity and extremely low aqueous solubility. It is freely soluble in ethanol (96%) and in methylene chloride. The active substance is light sensitive.

Fulvestrant exhibits stereoisomerism due to the presence of six chiral carbon atoms and a stereogenic sulfoxide in the side chain. The active substance is a mixture of 2 diastereoisomers: fulvestrant sulfoxide A and B. They have the same absolute configuration at each of the stereogenic centres in the steroid system but different absolute configurations at the sulphur atom. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has not been observed for fulvestrant.

As there is a monograph of fulvestrant in the European Pharmacopoeia (Ph. Eur.), the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for fulvestrant which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for appearance (visual), identity (specific optical rotation, IR), appearance of solution (Ph. Eur.), assay (HPLC), related substances (HPLC), stereochemical purity (chiral HPLC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), bacterial

endotoxins (Ph. Eur) and microbial limits (Ph. Eur.). Specifications have been set for residual solvents methanol, ethyl acetate and toluene tested using gas chromatography (included in the CEP).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 10 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5 ºC ± 3 ºC) and for 8 commercial scale batches for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identity (HPLC), water content, assay, related substances, stereochemical purity and microbiological stability. The analytical methods used are stability indicating.

All tested parameters were within the specifications and no trend was observed at either condition.

Photostability testing following the ICH guideline Q1B was performed on one batch and as part of forced degradation study. Fulvestrant is sensitive to light, both in solution and as powder, due to formation of some degradation products even after a short exposure time (30 minutes for solution and 8 hours for the powder). Therefore the active substance needs to be stored in suitably protective packaging. Results under stressed conditions (acid, base, oxidation, heat stressed conditions) were also provided. Fulvestrant is slightly sensitive to acid (plus temperature) after a prolonged exposure (72 hours at 60 °C with HCl). Fulvestrant is sensitive to base (plus temperature) when exposed for several hours (72 hours at 60 °C) and the oxidative product fulvestrant sulfone is formed. Fulvestrant is very sensitive to oxidation with an increase in fulvestrant sulfone up to about 9% after only 30 minutes. Fulvestrant is slightly sensitive to heat both in solution and as powder due to formation of some degradation products after a prolonged exposure time for the solution and after 24 hours at 105 °C for the powder.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months when stored at 5±3 ºC in the proposed container which comprises glass bottles in double polyethylene bags placed in a polyester/aluminium/polyester/polypropylene bag.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as solution for injection in a pre-filled syringe containing 250 mg of fulvestrant as active substance.

The finished product is a long-acting intramuscular depot formulation. The dosage form has been developed as a generic version of the centrally authorised product Faslodex which contains the same active substance in the same pharmaceutical form and is intended to be used *via* the same route of administration (intramuscular injection intended to be used once per month).

The pharmaceutical development of the finished product contains Quality by Design (QbD) elements.

As the finished product is a parenteral solution intended solely for administration by injection and contains the same active substance and excipients as the RMP, bioequivalence studies may not be required. However the sustained release properties of the formulation (and corresponding dosing regimen) is a critical element to assure bioequivalence. The quality and *in vivo* performance of the finished product are connected to both quantity and quality of the active substance and excipients, especially castor oil which contributes to the finished product viscosity and influences performance *in vivo* by modification of release rate. In order to demonstrate pharmaceutical equivalence of Fulvestrant Mylan and the RMP, extensive comparative studies were asked for by the CHMP during the assessment procedure and have been performed using multiple batches of both products. Comparative fatty-acid profile data between reference and generic products was also provided at the request of CHMP. The fatty acid profile of refined castor oil is similar to the profile of finished products, both reference and generic products. Overall, it can be concluded that the generic product contains the same quality and quantity of refined castor oil as the RMP. Therefore, the requirement of the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr with respect to the demonstration of the essential similarity of the oily solution for intramuscular administration is considered fulfilled.

Physicochemical characteristics of RMP Faslodex were evaluated and the results are considered adequate.

The formulation and manufacturing development were evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on prior knowledge of products with similar formulations and manufacturing processes as well as on experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility of excipients and the active substance has been confirmed through stability studies.

Aseptic processing followed by sterile filtration was chosen as the preferred method of sterilization based on publicly available information regarding the RMP. A terminal sterilization suitability study was performed. The analysis of description, assay, degree of colouration and related substances demonstrated that the proposed finished product is thermally unstable.

The primary packaging consists of a syringe and a plunger stopper. The syringe is a clear type 1 glass syringe containing an elastomeric tip cap and polycarbonate luer lock connector and a polypropylene plunger rod within a polypropylene tamper-evident closure. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A study was carried out to investigate the compatibility of the glass syringe barrel with elastomeric tip cap and the plunger stopper with the finished product solution. Results were found to comply with respect to the tested parameters after up to 6 months at accelerated conditions (25 ± 2 °C/ 60 ± 5% RH), demonstrating the compatibility of the finished product and container closure system.

A study was carried out to determine the potential extractables/leachables in the container closure system that could leach into the finished product solution over the shelf-life. The extraction experiment

performed on the elastomeric tip cap and the plunger stopper resulted in the maximum theoretical maximum daily intake (MDI) values that are lower than the staged TTC of 60 microgram/day. All the extractables observed from rubber stoppers of the Fulvestrant injection were far below the safety threshold of 60 microgram/day.

Functionality testing of the Fulvestrant Mylan syringes was performed on a single batch at release and end of shelf life and found to be acceptable.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: dispensing, compounding, sterile filtration, filling, and labelling and packaging. The process is considered to be a non-standard manufacturing process as it utilizes sterile filtration and aseptic filing to ensure sterility of the finished product. The primary container components are purchased pre-sterilised. The sterilisation methods for equipment that comes into contact with the product during processing are described and considered acceptable.

Major steps of the manufacturing process have been validated on 3 consecutive commercial scale batches representative of the proposed commercial manufacturing process. Operating steps that are critical to the manufacture of the finished product include dispensing, compounding, filtering and filling. To ensure product quality, each batch was sampled throughout the filtering, filling, and packaging operations and multiple physical inspections were carried out. Bioburden was assessed prior to the sterile filtration. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (in house), identification (HPLC, TLC), volume in container, uniformity of dosage units (Ph. Eur., in house), degree of coloration (in house), particulate matter (Ph. Eur.), viscosity (Ph. Eur.), content of free fatty acids (titration), water content (Ph. Eur.), optical clarity (Ph. Eur.), assay (HPLC), stereochemical purity (HPLC), related substances (HPLC), ethanol content (GC), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), initial force/ break loose force (force tester), mean dynamic glide force/ friction force (force tester), maximum dynamic glide force/ friction force (force tester) and minimum dynamic glide force/ friction force (force tester).

The viscosity specification was tightened during the assessment procedure as requested by the CHMP in order to ensure that this parameter is as close as possible to analysed reference medicinal product's batches.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released to the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of the finished product stored for up to 24 months (1 batch) and 18 months (2 batches) under long term conditions (2 - 8 ºC) and for up to 6 months under accelerated conditions (25 ± 2 °C / 60 ± 5% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification, degree of colouration, particulate matter, viscosity, content of free fatty acids, water content, optical clarity, assay, stereochemical purity, related substances, ethanol content, sterility, bacterial endotoxins, initial force/ break loose force, mean dynamic glide force/ friction force, maximum dynamic glide force/ friction force and minimum dynamic glide force/ friction force. The analytical procedures used are stability indicating.

Neither significant changes nor trends have been observed.

A 28 days in-use stability study was carried out on a single batch of the finished product in order to support temperature excursions that may occur over the shelf-life. The results are within the specification and no trends were observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were assessed for description, identity, degree of coloration, particulate matter, viscosity, content of free fatty acids, water content, optical clarity, assay, stereochemical purity, related substances and ethanol content. The finished product remained within the proposed shelf-life specifications following the photostability study. The result of this photostability study demonstrates that light has no impact on the quality of the finished product when stored inside the syringe. However taking into consideration the limited duration of the test, the recommendation proposed in the SmPC ("Store the pre-filled syringe in the original package in order to protect from light") is considered appropriate.

Forced degradation studies were performed during validation of the assay and related substances test methods. The finished product samples was stressed with acid (0.1N and 1.0N HCl), base (0.1N and 1.0N NaOH), heat (80 °C for 24h, 48h), oxidant (1%, 3%, 10% H_2O_2) and light (1.2 MW/m^2). Some degradation was observed on treatment with acid (0.1N HCl), 10% H_2O_2 oxidant, and light.

Based on available stability data, the proposed shelf-life of 24 months and storage conditions of "Store and transport refrigerated (2 °C – 8 °C). Temperature excursions outside 2 °C – 8 °C should be limited and not exceeding a 28 day period where the average storage temperature for the product is below 25 °C (but above 2 °C – 8 °C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2 °C – 8 °C). Temperature excursions have a cumulative effect on the product quality and the 28 day time period must not be exceeded over the duration of the shelf life of Fulvestrant. Exposure to temperatures below 2 °C will not damage the product providing it is not stored below – 20°C. Store the pre-filled syringe in the original package in order to protect from light." as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

As the finished product is a parenteral solution intended solely for administration by injection and contains the same active substance and excipients as the RMP, bioequivalence studies are not required. In order to demonstrate pharmaceutical equivalence of Fulvestrant Mylan and the RMP however, extensive comparative studies have been asked for by the CHMP during the assessment procedure and have been performed using multiple batches of both products.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (INN / Invented Name): Fulvestrant Mylan 250 mg solution for injection			
CAS-number (if available):			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- Partition Coefficient Octanol Water log P	OECD123	7.67	Potential PBT (Y/N)

PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	Log P	7.67			B/not B
	BCF	< 400			B/not B
Persistence	DT50 or ready biodegradability	≤ 14 days			P/not P
Toxicity	NOEC or CMR	Please see NOEC values below			T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.00113	µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			
Ready Biodegradability Test	OECD 301	0.0 gO_2/g			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 = <14 days (Total System)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	below limit of detection of 0.047 mg/L		*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	below limit of detection of 0.00003 mg/L		*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>100mg/L (nominal)		

2.3.3. Discussion on non-clinical aspects

The CHMP considers that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

The applicant provided an ERA as per CHMP request. This determined $PEC_{SURFACEWATER}$ value is approximately 10-fold below the action limit of 0.01 µg/L, indicating that fulvestrant use would have to increase the same approximate 10-fold above the current worst-case use scenario in order to exceed the PEC action limit and trigger a mandatory Phase II environmental fate and effect analysis. Using the highest average Fpen value (0.00552%) would generate a $PEC_{SURFACEWATER}$ value (0.00049 µg/L) that is approximately 20-fold below the 0.01 µg/L action limit. Thus, it is considered that the use and population data over the last 4 years across 27 different Member States provides adequate justification for the absence of specific ERA study data for the Fulvestrant Mylan 250 mg solution for injection submission and additional Phase II studies are not required. Since fulvestrant is a potential endocrine disruptor, the Applicant additionally addressed public domain data to make a scientifically sound assessment of the environmental risk, with a special interest to avoid unnecessary repetition of animal studies (e.g. fish). Physical chemistry data, bioconcentration data, aquatic toxicity and environmental fate data together with known metabolism of fulvestrant formed adequate justification of absence of the Phase II studies.

Based on the physico-chemical and environmental fate properties of fulvestrant, it is likely that any remaining active moiety (after extensive human metabolism) present in domestic sewage would be partitioned into the sewage sludge during wastewater treatment. Laboratory wastewater treatment simulation tests indicate that fulvestrant is completely degraded and is therefore unlikely to enter the aquatic or terrestrial environment. Finally, based upon the measured bioconcentration factor in fish (BCF < 400), the risk of bioaccumulation of fulvestrant in aquatic organisms is considered very low (BCF < 1000).

The ERA is considered acceptable.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.4. Conclusion on the non-clinical aspects

Overall, the non-clinical data and the ERA submitted in support of the authorisation of Fulvestrant Mylan 250 mg solution for injection are considered acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for solution for injection containing fulvestrant.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of fulvestrant based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version, is of particular relevance.

Exemption

There are no bioequivalence studies submitted with this application.

In accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), Appendix II, in the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required.

Fulvestran Mylan contains the same active substance in the same concentration as the reference product.

The Applicant provided information that the excipients contained in the proposed formulation are the same and in the same quantity as the ones contained in the reference product formulation.

Fulvestran Mylan and Faslodex are medicinal products for intramuscular administration as oily solution and as such are anticipated to be of similar bioavailability.

The justification for waiving bioequivalence studies is acceptable.

2.4.2. Pharmacokinetics

No new pharmacokinetics studies were presented and no such studies are required for this application.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

No bioequivalence studies were submitted with this application. In accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), Appendix II: In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required. The justification provided by the applicant for waiving bioequivalence studies is acceptable.

As the active substance fulvestrant is widely used and well-known, no further studies have been submitted which is considered acceptable. Fulvestrant has been used for postmenopausal women with hormone receptor-positive breast cancer more than 10 years and the safety profile and tolerability of the medicinal product is well established. Based on CONFIRM trial results, the 500 mg once-monthly dose of fulvestrant is now the approved dose in the European Union (approved in 2010).

Discussion on the recent scientific publications on the pharmacodynamics/pharmacokinetics and efficacy/safety of fulvestrant were included in the Clinical overview which is considered adequate.

The clinical parts of the Summary of Product Characteristics and Package leaflet are in line with that of Faslodex. The product information is also adequately reflecting excipients with known effect and relevant warnings in accordance with the excipients guideline.

2.4.6. Conclusions on clinical aspects

In conclusion, the benefits of Fulvestrant Mylan 250 mg/5 ml solution for injection are considered to outweigh the risks and authorisation can be recommended for the product.

2.5. Risk management plan

Safety concerns

Summary of the safety concerns

Table 2: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Thromboembolic events - Hepatic events - Injection site reactions - Hypersensitivity reactions Increased risk of bleeding at the injection site
Important potential risks	- Osteoporosis / Osteopenia - Ischaemic cardiovascular events - Endometrial dysplasia - Joint disorder - Interstitial lung disease - Vasculitis - Pulmonary microembolism of oily solutions Use in pregnancy and lactation
Missing information	- Safety and efficacy in children and Adolescents - Patients with severe hepatic impairment - Patients with severe renal impairment

The safety concerns as proposed by the Applicant in the risk management plan version 3.0 are acceptable.

Pharmacovigilance Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures for Fulvestrant

No additional risk minimisation measures are necessary.

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0, dated 03 October 2017, is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of fulvestrant solution for injection. The reference product Faslodex is indicated 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 anti-estrogen therapy, or disease progression on anti-estrogen therapy.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics, pharmacodynamics, efficacy and safety of the active substance. The applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fulvestrant Mylan is favourable in the following indication:

Fulvestrant is indicated 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 anti-estrogen therapy, or disease progression on antiestrogen therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.