EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Fertavid

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision issued [2] / amended on	Product Information affected [3]	Summary
WS/1702	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC in order to revise the safety information regarding Ovarian Hyperstimulation Syndrome (OHSS) to replace clinical advice describing specific interventions with	28/11/2019	20/01/2020	SmPC, Labelling and PL	Section 4.4 of the SmPC containing information on the special warnings and precautions for use was updated as per current knowledge in relation to the safety information regarding Ovarian Hyperstimulation Syndrome.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	the recommendation to follow current clinical practice for reducing the risk of OHSS during Assisted Reproductive Technology (ART), based on post-marketing data and literature review. The package Leaflet is updated accordingly. In addition, the worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet and made some editorial changes in the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0045	B.II.z - Quality change - Finished product - Other variation	25/07/2019	n/a		
WS/1502	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	16/05/2019	n/a		
IG/1062	A.7 - Administrative change - Deletion of manufacturing sites	11/02/2019	n/a		
WS/1457/G	This was an application for a group of variations following a worksharing procedure according to	13/12/2018	n/a		

	Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0968	A.7 - Administrative change - Deletion of manufacturing sites	28/09/2018	16/09/2019	Annex II and PL	
WS/1339/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	12/07/2018	n/a		
T/0039	Transfer of Marketing Authorisation	13/06/2018	06/07/2018	SmPC, Labelling and	

				PL	
PSUSA/1465/201705	Periodic Safety Update EU Single assessment - follitropin beta	30/11/2017	n/a		PRAC Recommendation - maintenance
WS/1186/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	13/07/2017	n/a		
WS/1124	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	21/04/2017	n/a		

N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/03/2017	28/04/2017	Labelling	
IG/0762	B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	26/01/2017	n/a		
IG/0730	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	10/10/2016	n/a		
WS/0975/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	15/09/2016	n/a		
IG/0703/G	This was an application for a group of variations.	18/07/2016	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/05/2016	28/04/2017	SmPC, Annex II, Labelling and PL	
IG/0545/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	27/04/2015	n/a		
WS/0691	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	26/03/2015	n/a		

	variation				
PSUV/0024	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
WS/0627	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a site where batch control/testing takes place for the finished product B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	20/11/2014	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/11/2014	19/02/2015	PL	
WS/0571/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes in the test procedure of the AS. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a	25/09/2014	n/a		Changes in the test procedure of the AS.

	biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0449/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	29/07/2014	n/a		
WS/0487/G	This was an application for a group of variations following a worksharing procedure according to	20/03/2014	n/a		

	Article 20 of Commission Regulation (EC) No 1234/2008. Changes to the manufacturing process of the finished product. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size				
R/0017	Renewal of the marketing authorisation.	18/12/2013	21/02/2014		Fertavid contains the active substance follitropin beta (INN), a recombinant human Follicle Stimulating Hormone (FSH) produced via recombinant DNA technology. FSH is normally produced and secreted by the anterior lobe of the pituitary gland. Deficient endogenous production of FSH may cause female and male infertility. In clinical studies comparing follitropin beta with urinary FSH for controlled ovarian stimulation, follitropin results in higher number of oocytes at a lower total dose and with a shorter treatment period when compared to urinary FSH. During the renewal reporting period there were no on-going or completed clinical studies with follitropin beta. All identified risks for Fertavid are adequately reflected in the current EU SmPC. The evaluation of the safety signal ovarian torsion identified during the renewal period resulted in an update to the SmPC to add a warning to Section 4.4. No new information related to any previously known risks were received during the renewal reporting period.

					During the reporting period of Fertavid renewal (2 May 2011 – 6 June 2015) no new clinical data became available which would impact the benefit-risk profile. Therefore the CHMP considers that risk benefit profile remains positive and the renewal can be granted with unlimited validity.
WS/0465	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Product Information (PI) to address common medical knowledge concerning assisted reproduction technology regarding : monitoring of ovarian response (SmPC section 4.2) ; updates regarding infertility evaluation before starting treatment, multiple pregnancy, ectopic pregnancy, ovarian hyperstimulation syndrome, ovarian torsion, ovarian and other reproductive system neoplasms, vascular complications, other medical conditions (SmPC section 4.4). The Package leaflet is updated accordingly. The MAH is taking the opportunity to update the PI in line with QRD template version 9 and to make other editorial corrections. In addition, the details of the local representative of Croatia have been included in the German, Greek, Spanish and Italian PL. C.I.4 - Change(s) in the SPC, labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	19/02/2015	SmPC, Annex II, Labelling and PL	The Company has updated the product information, and has referred to published literature and the QRD template to justify changes in the wording of sections 4.2, 4.4 and 4.6 of the SmPC. The Company has revised wording of section 4.2 and 4.4 of the SPC to reflect current clinical practice in the management of fertility that recommends use of ultrasound images to guide management with the medicinal product by following follicular development and by detecting multi-fetal gestations. The Company has introduced information to section 4.4 of the SmPC on management of the ovarian hyper-stimulation syndrome. The revised wording is acceptable and is considered to enhance clinical safety of patients. Grammatical changes have been made to sections 4.4, 4.6, 4.8 and 5 of the SmPC to improve clarity of meaning on use of the medicinal product and to comply with the QRD template; furthermore minor editorial corrections were made throughout the SmPC. These changes are also acceptable. The PL has been updated in order to reflect the SmPC changes described above. Overall, the changes to the product information texts are considered to improve clinical safety and so the benefit / risk balance of the current product in the stated indications remains as positive.

IA/0020/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	13/12/2013	21/02/2014	Annex II and PL	
IG/0366	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	08/11/2013	n/a		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/10/2013	21/02/2014	PL	
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
WS/0228/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to the control of the active substance B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	19/04/2012	n/a		

	material/intermediate/reagent - Other variation				
IA/0013/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	22/12/2011	21/02/2012	SmPC, Annex II, Labelling and PL	
IG/0117/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	18/11/2011	18/11/2011	Annex II	

T/0007	Transfer of Marketing Authorisation	22/07/2011	26/08/2011	SmPC, Labelling and PL	Transfer of Marketing Authorisation from Shering-Plough Europe to Merck, Sharp & Dohme Ltd.
WS/0112	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes to the manufacturing process of the drug product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	17/03/2011	17/03/2011		
WS/0072/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes to the active substance manufacturing process and control. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	17/03/2011	17/03/2011		

	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol				
WS/0034	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/10/2010	29/11/2010	SmPC, Labelling and PL	This type II variation concerns a safety update of the SPC following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Following a re-analysis of safety data a separate warning regarding ovarian torsion is included in the SPC Section 4.4. OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovaries have been identified as risk factors for ovarian torsion. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion. SPC Section 4.8 was amended by including the following adverse reactions in the table concerning treatment in females: abdominal discomfort, constipation, diarrhoea, metrorrhagia, ovarian cyst, ovarian torsion, uterine enlargement, vaginal haemorrhage (uncommon). Headache, rash and injection site pain (common) are included in the table concerning treatment in men. Minor changes in the labelling and other SPC sections (4.1; 4.2; 4.3; 4.6) and corrections of linguistic differences between the Puregon and Fertavid texts were also agreed. The PL is updated accordingly.
WS/0033	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/09/2010	28/10/2010	SmPC	Section 5.1 of the SmPC was amended to support the current information in Section 4.2. The information added to SmPC 5.1 shows a comparison to urinary FSH, including presentation of study data on (mean) total dosage and

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				treatment period needed. A minor change was also made to the text of SmPC section 4.2.
II/0006	Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/04/2010	02/06/2010	SmPC, Labelling and PL	The Fertavid Product Information was updated (in line with recent Puregon updated text) to comply with the SPC guideline and QRD template by using short terms for the pharmaceutical form in section 3 of the SPC and in section 6 of the Package Leaflet, by using abbreviated terms for the administration route in the Labelling as well as by harmonising the prefixes used in the Labelling. Also the Package Leaflet has been updated following the conduct of a Readability Testing on the vials Package Leaflet.
II/0004	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Changes to QPPV Update of DDPS (Pharmacovigilance)	20/01/2010	11/02/2010	Annex II	The DDPS has been updated to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated including the new version number (version 7) of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH is acceptable.
II/0005	Change to the purification process of the drug substance. Change(s) to the manufacturing process for the active substance	19/11/2009	19/11/2009		
II/0001	Changes to control of the active substance Change(s) to the test method(s) and/or specifications for the active substance	24/09/2009	05/10/2009		

IB/0002	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	04/08/2009	n/a		
IA/0003	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/07/2009	n/a	Annex II and PL	