GONAL-f

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
T/0140	Transfer of Marketing Authorisation	12/07/2018	03/08/2018	SmPC, Labelling and PL	
IB/0139	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	17/04/2018	03/08/2018	SmPC	

[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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

II/0138/G	This was an application for a group of variations. 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.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	15/06/2017	n/a		
II/0136	Update of the SmPC section 4.8 to indicate that thromboembolism can occur both in association with and separate from ovarian hyperstimulation syndrome (OHSS). In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/03/2017	01/03/2018	SmPC, Annex II, Labelling and PL	
IA/0137	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	27/02/2017	n/a		
IA/0134/G	This was an application for a group of variations.	01/09/2016	n/a		

	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IB/0135	B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	25/08/2016	n/a		
PSUSA/1463/ 201510	Periodic Safety Update EU Single assessment - follitropin alpha	09/06/2016	n/a		PRAC Recommendation - maintenance
IAIN/0133	B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product	30/03/2016	n/a		
IB/0130/G	This was an application for a group of variations.	01/02/2016	n/a		

	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products				
IA/0132/G	This was an application for a group of variations. 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 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	28/01/2016	n/a		
IB/0129	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	11/01/2016	13/12/2016	PL	
IG/0500	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	17/11/2014	n/a		
IG/0461	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	22/07/2014	n/a		

	(including contact details) and/or changes in the PSMF location				
IB/0126	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	13/05/2014	n/a		
IB/0125	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/04/2014	09/04/2015	SmPC, Annex II, Labelling and PL	
WS/0457	This was an application for a variation 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.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	18/12/2013	n/a		
IAIN/0124	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	13/12/2013	n/a		
IB/0121	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	11/11/2013	n/a		

IA/0123	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	31/10/2013	n/a		
N/0118	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/10/2013	09/04/2015	PL	
IB/0122	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	22/10/2013	n/a		
IG/0361	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/10/2013	n/a		
IB/0117	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	22/07/2013	n/a		
WS/0380	This was an application for a variation 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.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	30/05/2013	n/a		
IG/0224	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2012	n/a		

WS/0294	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to the control of the drug substance and drug product 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	20/09/2012	n/a		
WS/0275	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change to the control of the finished product B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	19/07/2012	n/a		
IB/0112	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	06/01/2012	n/a		
IB/0111	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/11/2011	28/06/2012	SmPC, Labelling and PL	
IG/0087	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change	18/07/2011	n/a		

	to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
IG/0076/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of 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	01/07/2011	n/a		
II/0109/G	This was an application for a group of variations. To register a new pen for presentations EU/1/95/001/033-035. To register a new site for the manufacture of the drug product. B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	14/04/2011	23/05/2011	SmPC, Labelling and PL	To register a new pen for presentations EU/1/95/001/033-035. To register a new site for the manufacture of the drug product.

IA/0110	A.7 - Administrative change - Deletion of manufacturing sites	23/05/2011	n/a		
IG/0069	A.7 - Administrative change - Deletion of manufacturing sites	12/05/2011	n/a		
R/0107	Renewal of the marketing authorisation.	20/05/2010	27/07/2010	SmPC, Annex II, Labelling and PL	
N/0108	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/04/2010	n/a	PL	
IA/0106	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/09/2009	n/a	Annex II	
IA/0105	IA_01_Change in the name and/or address of the marketing authorisation holder	11/09/2009	n/a	SmPC, Labelling and PL	
II/0102	To amend sections 4.2 and 5.1 of the SPC in response to the CHMP assessment report (November 2008) related a FUM. The PL is amended to update the details of the Local Representative in Spain. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	24/07/2009	SmPC and PL	Following the Assessment of a Follow-Up Measure (FUM) the MAH was requested by the CHMP to remove from section 4.2 “Posology and Method of administration” of the SPC the sentence relating to the efficacy of the r-FSH compared to u-FSH.. During this variation application the MAH applied to modify the section 4.2 of the SPC to remove the claim that recombinant FSH (r-FSH) is more effective than urinary FSH (u-FSH). In return the statement in section 4.2 was re-worded to present the fact that lower dose of r-FSH achieves the same result as the u-FSH. This statement was re-enforced by the re-submission of the data of three clinical studies (GF 8407, 22240 and 21884) and their observations

					as well as newly published bibliographic data. A reference in the section 4.2 to the section 5.1 was made where more details on the results of these studies and their clinical and statistical significance are given to the prescribers. The Package Leaflet has also been amended with the contact details of the local representative for Spain.
II/0104	Change to the stability protocol for the drug substance. Change(s) to shelf-life or storage conditions	29/05/2009	11/06/2009		
II/0101	Additional site for Quality Control testing of the drug substance. Change of reference standard. Change(s) to the test method(s) and/or specifications for the active substance	29/05/2009	11/06/2009		
IA/0103	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	26/03/2009	n/a	Annex II and PL	
N/0099	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/01/2009	n/a	Labelling and PL	
IB/0100	IB_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	19/11/2008	n/a		
IA/0098	IA_05_Change in the name and/or address of a	13/10/2008	n/a	Annex II and PL	

	manufacturer of the finished product				
IA/0097	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/10/2008	n/a	Annex II	
IA/0096	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	04/07/2008	n/a		
II/0093	Quality changes	30/05/2008	05/06/2008		
IA/0095	IA_28_Change in any part of primary packaging material not in contact with finished product	21/05/2008	n/a		
IA/0094	IA_05_Change in the name and/or address of a manufacturer of the finished product	15/04/2008	n/a		
II/0091	Change(s) to shelf-life or storage conditions	15/11/2007	21/12/2007	SmPC, Labelling and PL	
N/0090	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/10/2007	n/a	PL	
IA/0089	IA_28_Change in any part of primary packaging material not in contact with finished product	08/08/2006	n/a	Labelling and PL	
IB/0088	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	31/07/2006	n/a		
II/0085	This variation relates to an update of section 4.8 of the	01/06/2006	20/07/2006	SmPC and PL	The MAH provided CHMP with a cumulative review of all

	Summary of Product Characteristics in relation to allergic reactions following CHMP request further to the assessment of the FUM 028. The Package Leaflet (section 4) was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				cases of allergic reactions since 1995 and a causality assessment of the serious cases within 2 months after the renewal. The MAH have received 57 reports of allergic reactions. Out of these 10 were serious. The CHPM considered that the majority of reactions were broadly covered by the mild reactions already listed in section 4.8, but that some additions were necessary and the SPC has updated (section 4.8) to reflect these changes. The Package Leaflet (section 4) was updated accordingly.
II/0081	Change(s) to the manufacturing process for the active substance	01/06/2006	26/06/2006	Annex II	
II/0080	Change(s) to the manufacturing process for the active substance	01/06/2006	07/06/2006		
II/0084	This variation concerns an update of section 4.8 of the Summary of Product Characteristics to add varicocele and injection site reaction in men following the assessment of long term data from male population treated for isolated hypogonadotrophic hypogonadism. These adverse reactions were also added to section 4 of the Package Leaflet (PL). In addition, the MAH updated section 3 of the PL for pre-filled pen to improve its safe use, and updated the Annexes according to the current version 7 of the QRD template. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/03/2006	10/05/2006	SmPC, Annex II, Labelling and PL	The CHMP recommended that varicocele in males should be added to the section 4.8 of the SPC as "common" adverse reactions occurring in >1/100 to <1/10 clinical trial cases (there were 7 cases of varicocele from 6 patients including one serious case) in clinical trials with GONAL-f. The MAH was also requested to add injection site reaction as a "very common" (>1/10) adverse reaction in men, as this reaction was only described as occurring in females in the section 4.8 of the SPC. These adverse reactions were also added to section 4 of the Package Leaflet. The MAH also took this opportunity to include a sentence in the section 3 of the PIL of the GONAL-f pre-filled pen to improve its safe use, and to update the Annexes according to the current version 7 of the QRD template.
IB/0086	IB_07_c_Replacement/add. of manufacturing site: All	08/05/2006	n/a		

	other manufacturing operations ex. batch release				
II/0079	Change(s) to the manufacturing process for the finished product	27/04/2006	03/05/2006		
II/0083	Change(s) to the manufacturing process for the finished product	23/02/2006	28/02/2006		
R/0078	Renewal of the marketing authorisation.	27/07/2005	19/10/2005	SmPC, Annex II, Labelling and PL	test because this won't work either, although Kevin says otherwise.
IB/0076	IB_37_a_Change in the specification of the finished product - tightening of specification limits	11/05/2005	n/a		
II/0072	Update of the sections 4.4, 6.5, 6.6 of the Summary of Product Characteristics (SPC) and sections 2, 3, 6 of the Package Leaflet (PL). Update of Summary of Product Characteristics, Labelling and Package Leaflet	17/03/2005	25/04/2005	SmPC, Labelling and PL	The Marketing Authorisation Holder (MAH) has applied for an update of section 4.4 of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) to include a warning for patients with porphyria or a family history of porphyria in compliance with the CHMP conclusions on the 12th PSUR. The MAH also applied for descriptive changes of the crimp cap in section 6.5 of the SPC for the pre-filled pen presentation and proposed to clarify administration instructions of multidose presentations for self-users: the MAH therefore applied for changes to sections 4.4, 6.6 of the SPC, sections 2 and 3 of the PL and section 5 of the outer packaging for the multidose presentations. In addition the contact details of the Danish and Greek local representatives in section 6 of the PL have been updated.

IA/0077	IA_09_Deletion of manufacturing site	14/04/2005	n/a		
IB/0075	IB_37_a_Change in the specification of the finished product - tightening of specification limits IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	22/03/2005	n/a		
IB/0071	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	05/01/2005	n/a		
IA/0070	IA_28_Change in any part of primary packaging material not in contact with finished product	16/12/2004	n/a		
IA/0069	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	16/12/2004	n/a		
IA/0068	IA_28_Change in any part of primary packaging material not in contact with finished product	16/12/2004	n/a		
IA/0067	IA_05_Change in the name and/or address of a manufacturer of the finished product	15/12/2004	n/a		
IA/0066	IA_05_Change in the name and/or address of a manufacturer of the finished product	06/10/2004	n/a		
IB/0065	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	29/06/2004	n/a	SmPC	
IB/0064	IB_20_c_Change in test procedure for an excipient - other changes	24/05/2004	n/a		

X/0059	X-3-iv_Change or addition of a new pharmaceutical form	25/09/2003	23/02/2004	SmPC, Labelling and PL	
II/0060	New presentation(s)	25/09/2003	14/01/2004	SmPC, Labelling and PL	
I/0062	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/10/2003	23/10/2003		
I/0061	31_Change in container shape	10/10/2003	10/10/2003	SmPC	
I/0063	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	20/08/2003	22/09/2003		
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2003	24/03/2003	PL	
I/0057	20_Extension of shelf-life as foreseen at time of authorisation	22/01/2003	22/01/2003		
I/0056	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	18/12/2002	20/12/2002		
I/0055	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	04/10/2002	11/10/2002		
I/0053	02_Change in the name of the medicinal product (either invented name of common name)	21/08/2002	02/10/2002	SmPC, Labelling and PL	

II/0049	Change(s) to the test method(s) and/or specifications for the active substance	19/09/2002	27/09/2002		
I/0054	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/08/2002	10/09/2002		
I/0051	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	18/07/2002	19/07/2002		
I/0052	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	16/07/2002	17/07/2002		
I/0050	01_Change in the name of a manufacturer of the medicinal product	09/07/2002	09/07/2002		
II/0048	Change(s) to the test method(s) and/or specifications for the active substance	27/06/2002	28/06/2002		
II/0040	Change to replace the currently registered ampoules containing the water for injections by vials to improve suitability of the product for patients. Change(s) to container	13/12/2001	07/06/2002	SmPC, Labelling and PL	
II/0039	Addition of methionine and polysorbate 20 as excipients, to improve the stability of the product and to reduce the rate of oxidation. Change in formulation	13/12/2001	07/06/2002	SmPC, Labelling and PL	
II/0038	Change to formulate and fill the medicinal product by mass (based on protein) rather than by definition of	13/12/2001	07/06/2002	SmPC, Labelling and	Based on the provided data, a conversion factor of 75 IU (target bioavailability) to 5.46 micrograms was determined.

	activity (IU) (based on bioassay). As a result, the quantity of active substance and strength are defined in mass units, where Gonal-F 37.5IU, 75 IU, 150 IU, and 600 IU/ml are expressed as Gonal-F 2.5, 5, and 10 micrograms, and 40 micrograms/ml respectively. Change(s) to the manufacturing process for the finished product			PL	The quality of the product is not affected by this variation. Gonal-F is dual labelled: mass as the primary unit and International Units. It is considered necessary to include both mass and IU on product information/labels, at least until users are familiarised with the new units.
II/0037	Replacement of the currently registered ampoule containing the Gonal-F powder with a vial presentation for the Gonal-F 37.5 IU presentations to improve suitability of the product for patients. Change(s) to container	13/12/2001	07/06/2002	SmPC, Labelling and PL	
X/0041	Addition of new presentations with the solvent presented in prefilled syringes. X-3-iv_Change or addition of a new pharmaceutical form	13/12/2001	06/06/2002	SmPC, Labelling and PL	The new presentations of the solvent consists of 1.1 ml sterilised water for injections (Ph.Eur.) in pre-filled syringes (Type I Ph.Eur. colourless glass). Pack sizes are: 1, 5, and 10 pre-filled syringes. Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of these new presentation is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the new presentations have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications.
II/0044	New presentation(s)	13/12/2001	06/06/2002	SmPC,	

				Labelling and PL	
I/0047	20_Extension of shelf-life as foreseen at time of authorisation	11/01/2002	19/02/2002	SmPC	
I/0046	23_Change in storage conditions	13/11/2001	28/01/2002	SmPC, Labelling and PL	
I/0045	03_Change in the name and/or address of the marketing authorisation holder	21/09/2001	07/11/2001	SmPC, Labelling and PL	
II/0030	Update of or change(s) to the pharmaceutical documentation	19/09/2001	24/09/2001		
I/0036	17_Change in specification of the medicinal product	20/07/2001	n/a		
I/0035	25_Change in test procedures of the medicinal product	20/07/2001	n/a		
I/0034	20_Extension of shelf-life as foreseen at time of authorisation	17/04/2001	20/07/2001	SmPC	
I/0033	10a_Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms	17/05/2001	20/07/2001	SmPC, Labelling and PL	
I/0032	01_Change following modification(s) of the manufacturing authorisation(s)	09/04/2001	20/07/2001		
I/0043	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	18/06/2001	06/07/2001		

II/0027	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	20/06/2001	SmPC, Labelling and PL	
II/0026	Extension of Indication	01/03/2001	20/06/2001	SmPC and PL	
I/0031	20_Extension of shelf-life as foreseen at time of authorisation	12/01/2001	05/03/2001	SmPC	
II/0028	Change(s) to the test method(s) and/or specifications for the finished product	25/01/2001	30/01/2001		
X/0022	X-3-iii_Addition of new strength	21/09/2000	29/01/2001	SmPC, Annex II, Labelling and PL	
R/0025	Renewal of the marketing authorisation.	21/09/2000	29/12/2000	SmPC, Annex II, Labelling and PL	
I/0029	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/12/2000	n/a		
I/0020	12_Minor change of manufacturing process of the active substance	29/06/2000	n/a		
I/0023	01_Change following modification(s) of the manufacturing authorisation(s)	07/01/2000	16/03/2000	Annex II and PL	
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/01/2000	16/03/2000	PL	

N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/10/1999	08/12/1999	PL	
I/0019	16_Change in the batch size of finished product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	24/06/1999	02/09/1999		
X/0015	X-3-iii_Addition of new strength	25/02/1999	18/06/1999	SmPC, Annex II, Labelling and PL	
II/0018	Update of Summary of Product Characteristics and Package Leaflet	25/02/1999	16/06/1999	SmPC, Labelling and PL	
II/0017	Extension of Indication	25/02/1999	16/06/1999	SmPC and PL	
II/0014	Change(s) to the test method(s) and/or specifications for the finished product	22/07/1998	02/09/1998		
II/0010	Change(s) to the test method(s) and/or specifications for the active substance	22/07/1998	02/09/1998		
I/0009	14_Change in specifications of active substance 24_Change in test procedure of active substance	22/07/1998	02/09/1998		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/06/1998	17/07/1998	PL	
I/0011	24_Change in test procedure of active substance	27/05/1998	n/a		
I/0013	24_Change in test procedure of active substance	17/05/1998	n/a		

I/0012	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	17/05/1998	n/a		
I/0008	24_Change in test procedure of active substance	17/12/1997	n/a		
I/0007	24_Change in test procedure of active substance	17/12/1997	n/a		
I/0006	01_Change following modification(s) of the manufacturing authorisation(s)	08/07/1997	30/09/1997	SmPC, Labelling and PL	
I/0005	12_Minor change of manufacturing process of the active substance	23/07/1997	n/a		
I/0003	20_Extension of shelf-life as foreseen at time of authorisation	16/10/1996	20/01/1997	SmPC	
I/0004	12_Minor change of manufacturing process of the active substance	12/09/1996	n/a		
II/0001	Extension of Indication	14/02/1996	28/06/1996	SmPC, Labelling and PL	
I/0002	15_Minor changes in manufacture of the medicinal product	02/02/1996	n/a		