PROCEDURAL STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 July 2004 please refer to module 8B.

At the time the initial positive opinion was granted, the CPMP considered that the scientific knowledge for products made using biotechnology is not static due to the rapidly evolving methodology in this field of science. Therefore new information will usually be generated on an ongoing basis after Marketing Authorisation is granted. The CPMP should be kept informed about any new data. The company fulfilled its commitment to submit to the EMEA before 31 October 1995 the final report of the *in vitro* fertilisation study performed in the United States of America. The CPMP considered the results to be satisfactory confirming the safety and efficacy of Gonal-F.

Although the pharmaceutical/biotechnological quality of the Gonal-F dossier has been proven sufficient to support marketing at this stage, there were a number of open points concerning biopharmaceutical characteristics and validation of some of the new methodologies used in the production process of Gonal-F. To this end also new testing methods should be developed. The company has agreed with the CPMP to provide within 6 to 12 months, depending on the case, appropriate information on the quality points identified during the Assessment (See chapter III.2). These follow-up measures have been addressed with submissions on 30 April 1996, 17 October 1996, 6 June 1997, 9 January 1998 and 31 March 2001.

Following the positive opinion on the new indication: anovulation (including polycystic ovarian disease) in women who have been unresponsive to treatment with clomiphene citrate, the CPMP requested the company to submit the results of additional ongoing clinical studies relating to the new indication . The additional results were submitted on 13 March 1998 and were found satisfactory.

Extensions / Major Variations

- New strength: Gonal-F 37.5 IU

On 25 February 1999, the CPMP issued a positive opinion for the new strength Gonal-F 37.5 IU. The procedure started on 29 May 1998. Although the SPC recommended a 37.5 IU dose titration for anovulatory indications, such strength was not available. Inclusion of the 37.5 IU strength will eliminate wastage, will facilitate adjustment of the treatment, and will minimise the chance of dosage mistakes as a result of the use of a fraction of previous dosage strengths. The Commission Decision for this extension was issued on 18 June 1999.

- New strength: Gonal-F 600 IU/ml (multidose presentation)

On 21 September 2000, the CPMP issued a positive opinion for the addition of a new strength Gonal-F 600 IU/ml. The procedure started on 17 December 1999. This new strength is a multidose presentation of Gonal-F and provides improved convenience for patients who are self-dosing at home. It also simplifies treatment tailoring, allowing dose titration by adapting the volume to be injected. This multidose vial containing preservative is not to be shared amongst patients; therefore it should be used by one patient only (as stated in the SPC). The Commission Decision for this extension was issued on 29 January 2001.

- Addition of new monodose presentations with the solvent presented in pre-filled syringes

On 13 December 2001, the CPMP issued a positive opinion for the addition of new monodose presentations with the solvent presented in prefilled syringes. The new presentations of the solvent consist 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. The Commission Decision for this Type II variation was issued on 7 July 2002.

- Addition of a new pharmaceutical form

On 25 September 2003, the CPMP considered that the benefit/risk profile of a new pharmaceutical form for GONAL-f (i.e. solution for injection presented in a pre-filled pen) was favourable. A positive opinion was therefore adopted on the addition of this new pharmaceutical form, a ready-to-use formulation designed to facilitate the administration of the product. The Commission Decision for this extension was issued on 23 February 2004.

- Addition for a new multidose presentation

On 25 September 2003, the CPMP adopted a positive opinion for a Type II for a new multidose presentation for GONAL-f powder and solvent for solution for injection 300 IU/0.50 ml (22 micrograms/0.50ml). After reconstitution with 0.75 ml of solvent, its concentration is the same as for the already authorised multidose presentations i.e. 600 IU/ml. The Commission Decision for this variation was issued on 14 January 2004.

Renewal of the Marketing Authorisation

For the first renewal of Gonal-F, the CPMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continued to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Gonal-F continued to be favourable for the authorised indications and issued on 21 September 2000 a positive opinion for the renewal of the Marketing Authorisation. The Commission Decision for this Renewal was issued on 29 December 2000.

Variations and notifications

All variations and notifications agreed upon after granting the Marketing Authorisation are summarised in the table below.

Scope	Type of modification	Procedure Start Date	Notification/ Opinion Date	CPMP opinion	Change in Comm. Decision	Date of Comm. Decision
Transfer of MAH to Ares-Serono Europe Ltd	Transfer[1]		20.12.95	N/A	Annex II	11.07.96
Additional site performing the bioassay on the active substance and the medicinal product	I [2] I/0002	15.12.95	02.02.96	Change accepted	-	
New indication: anovulation in women (including polycystic ovarian disease, PCOD) who have been unresponsive to treatment with clomiphene citrate.	II II/0001	13.12.95	14.02.96	Change accepted	Annex I & III	28.06.96
Minor change in the manufacturing process of the active substance	I / II I/0004	02.07.96	12.09.96	Change accepted	-	-
Extension of shelf-life from 1 to 2 years as foreseen at the time of authorisation	I / II I/0003	23.05.96	16.10.96	Change accepted	Annex I	20.01.97
Change of the address of the Marketing Authorisation Holder	I I/0006	09.06.97	08.07.97	Change accepted	Annex II	30.09.97
Minor change to the manufacturing process of the active substance	I / II I/0005	30.05.97	23.07.97	Change accepted	-	
Change in the test procedure for the active ingredient (two variations)	I / II I/0007 I/0008	21.11.97	17.12.97	Change accepted	-	06.01.98
Change in the test procedure for the active ingredient	I / II I/0009	30.01.98	22.07.98	Change accepted	-	02.09.98 Letter
Change in the test procedure for the active ingredient with consequential change in the specifications of the active substance	II II/0010	30.01.98	22.07.98	Change accepted	-	02.09.98 Letter
Change in the test procedure for the active substance	I / II I/0011	27.03.98	27.05.98	Change accepted	-	
Change in the test procedure for the active substance and the medicinal product	I / II I/0012	27.03.98	27.05.98	Change accepted	-	
Minor change in the manufacturing process of the active substance and consequential change in batch size of the active substance	I / II I/0013	27.03.98	27.05.98	Change accepted	-	
Change in the address of Greek and Austrian representatives	Notification [3] N/0016	16.03.98	05.06.98	N/A	Annex III	17.07.98
Change in the specifications of the medicinal product	II II/0014	29.05.98	22.07.98	Change accepted	-	02.09.98 Letter

[1] Transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.

[2] I refers to a minor variation (type I variation); II refers to a major variation (type II variation); I / II refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation.

[3] Notification in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992.

Scope	Type of modification	Procedure Start Date	Notification/ Opinion Date	CPMP opinion	Change in Comm. Decision	Date of Comm. Decision
Addition of New Indication Male hypogonadotropic hypogonadism	II II/0017	18.12.98	25.02.99	Change accepted	Annex I & III	16.06.99
Update of SPC according to new scientific information and revision of SPC, Labelling and Leaflet	II II/0018	18.12.98	25.02.99	Change accepted	Annex I & III	16.06.99
Increase in batch size	I/0013		27.05.98	Change accepted	-	-
Additional manufacturing site for the finished product	I/II I/0019	29.01.99	24.06.99	Change accepted	-	09.07.99 Letter
Line extension: Gonal-f 37.5 IU	X/0015		25.02.99	Change accepted	Annex. I, II & III	18.06.99
New indication: Hypo Males	II/0017		25.02.99	Change accepted	Annex I, & III	16.06.99
Changes in the SPC text on relative potency	II/0018		25.02.99	Change accepted	Annex I & III	16.06.99
Minor change of the manufacturing process of the active substance	I/II I/020	30.07.99	29.06.00	Change accepted	-	02.08.00 Letter
Change in the local representative for UK and Ireland (package leaflet)	N/0021 Notification[3]	17.09.99	14.10.99	Change accepted	Annex III	08.12.99
Change in the name of the finished product manufacturer	I I/0023	06.12.99	07.01.00	Change accepted	Annex II & III	16.03.00
Change in the local representative for Portugal and Greece (package leaflet)	N/0024 Notification[3]	20.12.99	07.01.00	Change accepted	Annex III	16.03.00
Line extension: Gonal-f 600 IU multidose	X/0022		21.09.00	Change accepted	Annex I, II & III	29.01.01
Renewal of Marketing Authorisation	R/0025	28.07.00	21.09.00	Accepted		29.12.00
New indication in FSH and LH deficient female	II II/0026	17.11.00	01.03.01	Change accepted	Annex I & III	20.06.01
Update of SPC	II II/027	17.11.00	01.03.1	Change accepted	Annex I & III	20.06.01
Change in specifications of the water for injections	II II/028	17.11.00	25.01.01	Change accepted	-	30.01.01 Letter
Addition of an alternative manufacturer for the water for injections	I I/0029	17.11.00	15.12.00	Change accepted	-	30.01.01 Letter
Demonstration of TSE compliance	II II/030	15.12.00	19.09.01	Change accepted	-	24.09.01 Letter
Extension of shelf life for Gonal-F 37.5 IU	I I/0031	15.12.00	12.01.00	Change accepted	Annex I	05.03.2001
Addition of an alternative packaging site	I I/0032	15.03.01	09.04.01	Change accepted		03.05.01
Addition of measuring device (multidose presentation)	I I/0033	20.03.01	17.05.01	Change accepted	Annex I & III	20.07.2001
Extension of shelf-life to 24 months for multidose presentation	I I/0034	16.03.01	17.04.01	Change accepted	Annex I	20.07.2001
Change in the test procedure of the medicinal product	I I/0035	27.04.01	20.07.01	Change accepted	-	27.07.01 Letter
Change in the specifications of the medicinal product	I I/0036	27.04.01	20.07.01	Change accepted	-	25.07.01 Letter
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	II II/0037	27.04.01	13.12.2001	Change accepted	Annex I & III	07.06.2002
Change to formulate and fill the medicinal product by mass (based on protein) rather than by definition of 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	II II/0039	27.04.01	13.12.2001	Change accepted	Annex I & III	07.06.2002
Addition of methionine and polysorbate 20 as excipients, to improve the stability of the product and to reduce the rate of oxidation	II II/0039	27.04.01	13.12.2002	Change accepted	Annex I & III	07.06.2002
Change to replace the currently registered ampoules containing the water for injections by vials to improve suitability of the product for patients	II II/0040	27.04.01	13.12.2001	Change accepted	Annex I & III	07.06.2002

Scope	Type of modification	Procedure Start Date	Notification/ Opinion Date	CPMP opinion	Change in Comm. Decision	Date of Comm. Decision
Change in specification of starting material/intermediate used in manuf. of the active substance	I I/0043	31.05.01	18.06.2001	Change accepted	-	06.07.01 Letter
Addition of a new pack size of the multidose presentation for Gonal-F with a concentration of 30 micrograms/ 0.75ml (450IU/ 0.75ml) for patient convenience. The concentration remains the same as the multidose presentation previously authorised	II II/0044	24.08.01	13.12.2001	Change accepted	Annex I & III	07.06.2002
Change in the name and/or address of the marketing authorisation holder	I I/0045	10.09.01	21.09.2001	Change accepted	Annex I & III	07.11.2001
Change in storage conditions	I I/0046	11.09.01	13.11.2001	Change accepted	Annex I & III	28.01.2002
Extension of shelf-life as foreseen at time of authorisation	I I/0047	12/12/2001	11.01.2002	Change accepted	Annex I	19.02.2002
Solvent in pre-filled syringes	X/0041	24.04.01	13.02.01	Change accepted		07.06.02
Change test procedure of active substance	II/0048	26.04.02	27.06.03	Change accepted		28.06.02 Letter
Change in the name of a manufacturer of the medicinal product	I/0050	10/06/2002	09.07.2002	Change accepted		09.07.02 Letter
Change in drug substance in-process controls	II/0049	31.05.02	19.09.02	Change accepted		27.09.02
Change in test procedure of active substance Change in test procedures of the medicinal product	I/0051	20/06/2002	18.07.2002	Change accepted	-	19.07.02 Letter
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0052	18/06/2002	16.07.2002	Change accepted	-	17.07.02 Letter
Change in the name of the medicinal product (either invented name of common name)	I/0053	22/07/2002	21/08/2002	Change accepted	Annex I & IIIA/B	02.10.02
Change in supplier of an intermediate compound used in manufacture of the active substance	I/0054	22/07/2002	20/08/2002	Change accepted		10.09.02 Letter
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0055	05/09/2002	04/10/2002	Change accepted		11.10.02 Letter
Change in specification of starting material/intermediate used in manuf. of the active substance	I/0056	15/10/2002	18/12/2002/	Change accepted		20.12.02 Letter
Extension of shelf-life as foreseen at time of authorisation	I/0057	23/12/2002	22/01/2003	Change accepted		22 01 03 Letter
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/0058[4]	23/01/2003	13/02/2003		Annex IIIB	24.03.03
Addition of new multidose presentation.	II/0060	23/05/2003	25/09/2003		Annex I & IIIA/B	14.01.04
Change in container shape	I/0061	23/07/2003	10/10/2003	Change accepted	Annex I	15.12.03 Letter
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0062	23/07/2003	10/10/2003	Change accepted		23.10.03 Letter
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0063	24/07/2003	20/08/2003	Change accepted		22.09.03 Letter
Line extension: new formulation (pre-filled pen)	X/0059	24.02.03	25.09.03	Change accepted		23.02.04
Change in test procedure for an excipient	IB/64	19.04.04	24.05.04	Change accepted		24 05 04 Letter
Change in shelf-life of finished product	IB/65	26.05.04	29.06.04	Change accepted	Annex I	29 06 04

[4] Notification in accordance with 61(3) of Council Directive 2001/83/EC as amended