STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- The Marketing Authorisation Holder submitted to the EMEA on 28 August 1997 an application for three type I variations falling within the scope of item No. 11 and item No. 16 of Annex I to Commission Regulation (EC) No 542/95. The Marketing Authorisation Holder applied for:

  1. Change in the manufacturers involved in the manufacture of the active substance, i.e. the addition of another manufacturer, Omnichem N.V. (Belgium).
  2. Change in the manufacturers involved in the manufacture of the active substance, i.e. the addition of another manufacturer, Squibb Manufacturing Inc. (Puerto Rico).
  3. Increase in the granulation batch size for the finished product intended for marketing.

  On 4 September 1997, the EMEA approved the variations. These variations did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted to the EMEA on 10 September 1997 an application for one type I variation falling within the scope of item No. 11 of Annex I to Commission Regulation (EC) No 542/95. The Marketing Authorisation Holder applied for:

  Change in the manufacturers involved in the manufacture of the active substance, i.e. the addition of another manufacturer, Orgamol SA (Switzerland).

  On 17 October 1997, the EMEA approved the variation. This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted to the EMEA on 12 January 1998 an application for one type I variation falling within the scope of item No 12 of Annex I to Commission Regulation (EC) No 542/95. The Marketing Authorisation Holder applied for:

  A minor change of the manufacturing process of the active substance

  On 20 February 1998, the EMEA approved the variation. This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted to the EMEA on 08 June 1998 an application for one type I variation falling within the scope of item No 11 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  An alternative manufacturer for the active substance.

  On 07 August 1998, the EMEA approved the variation. This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted to the EMEA on 22 September 1998 an application for one type I variation falling within the scope of item No 15 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  A change in the manufacture of the medicinal product, specifically an alternative powder transferring process.

  On 23 October 1998, the EMEA approved the variation. This variation did not require amendments to the Commission Decision.

- On 25 September 1998 The Marketing Authorisation Holder submitted a Type II variation application in accordance with Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation related to the update in the SPC and PL according to the irbesartan-specific information provided in the CoAprovel positive opinion. The wording of the legal status has also been updated in Annex II of the Commission decision.

  On 17 December 1998 the CPMP approved the variation. The variation required amendments in the relevant sections of the Commission Decision and the EPAR. The European Commission amended the Decision on 13 April 1999. In addition, the scientific discussion on efficacy of the EPAR was updated with more detailed information.

- The Marketing Authorisation Holder submitted to the EMEA on 30 September 1998 an application for one type I variation falling within the scope of item No 3 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  A change in the address of the marketing authorisation holder.

  On 05 November 1998, the EMEA approved the variation. The variation required amendments in the relevant sections of the Commission decision. The respective Commission Decision was issued on 23 February 1999.

- The Marketing Authorisation Holder submitted to the EMEA on 18 December 1998 an application for one type I variation falling within the scope of item No 11b of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  An alternative manufacturer for one step of the manufacturing process of the active substance.

  On 20 January 1999, the EMEA approved the variation. This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted to the EMEA on 24 March 1999 an application for one type I variation falling within the scope of item No 1 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  An authorisation of a second European site responsible for batch release for the EU.

  On 28 April 1999, the EMEA issued the corresponding notification. This variation required amendments to the Commission Decision. The respective Commission Decision was issued on 16 June 1999.

- The Marketing Authorisation Holder submitted to the EMEA 26 April 1999 an application for one type I variation falling within the scope of item No 12a of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  Changes in the specification of starting material used in the manufacture of the active substance.

  On 1 June 1999, the EMEA issued the corresponding notification. This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted to the EMEA 5 August 1999 an application for one type I variation falling within the scope of item No 11b of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  An alternative supplier of an intermediate compound used in the manufacture of the active substance.

  On 8 September 1999, the EMEA issued the corresponding notification. This variation did not require amendments to the Commission Decision.

- On 8 September 1999 The Marketing Authorisation Holder submitted a Type II variation application in accordance with Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation related to the update in the SPC and PL according to the irbesartan post-marketing experience and new pharmacokinetic data. In addition, on 3 December 1999, the MAH applied for changes of the Representative of the Aprovel Marketing Authorisation Holder following the merger of Sanofi and Synthelabo.

  On 16 December 1999 the CPMP approved the variation. The variation required amendments in the relevant sections of the Commission Decision and the EPAR. The European Commission amended the Decision on 25 April 2000.

- The Marketing Authorisation Holder submitted to the EMEA 19 November 1999 an application for one type I variation falling within the scope of item No 12 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for:

  A minor change in the manufacturing process of the active substance.

  On 21 December 1999, the EMEA issued the corresponding notification. This variation did not require amendments to the Commission Decision.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
Update of Summary of Product Characteristics and Package Leaflet The SPC was updated following the assessment of the 4th PSUR.	II/17	II	27.07.00	14.11.00
Extension of shelf-life of the active substance as foreseen at time of authorisation	I/18	I	26.10.00	15.01.01
Change in test procedure for starting material/intermediate used in manuf. of active substance	I/19	I	21.11.00	N/A
Update of Summary of Product Characteristics and Package Leaflet The SPC was updated regarding the information in case of pregnancy.	II/20	II	14.12.00	23.04.01
Changes to comply with supplements to pharmacopoeias	I/21	I	20.03.01	26.03.01
Minor change of manufacturing process of the active substance	I/22	I	26.04.01	02.05.01
Update of the SPC and PL (Point 4.5, 4.8, 6.5)	II/23	II	20.09.01	10.04.02
Change in pack size for a medicinal product	I/24	I	13.07.01	08.10.01
Change in pack size for a medicinal product	I/25	I	13.07.01	08.10.01
Change in pack size for a medicinal product	I/26	I	13.07.01	08.10.01
Change in pack size for a medicinal product	I/27	I	20.09.01	
Change in pack size for a medicinal product	I/28	I	20.09.01	
Extension of the Indication	II/29	II	27.02.02	12.06.02
Change in pack size for a medicinal product	I/30	I	20.09.01	
Replacement of an excipient with a comparable excipient	I/31	I	12.10.01	
Change in the manufacturing authorisation	I/32	I	11.01.02	11.04.02
Change in batch size of finished product	I/33	I	26.11.01	
Change in the manufacturing authorisation	I/34	I	22.12.01	08.03.02
Change in the test procedure for starting material/intermediate used in manufacturing of active substance	I/35	I	10.04.02	02.05.02
Change in the test procedure for starting material/intermediate used in manufacturing of active substance	I/36	I	10.04.02	30.04.02
Renewal	R/37	R	25.07.02	29.10.02
Change in the manufacture of the medicinal product	I/38	I	05.06.02	18.06.02
Minor change of manufacturing process of the active substance	I/39	I	19.12.02	17.01.03
Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/40	N	17.01.03	07.03.03
Update of Summary of Product Characteristics and Package Leaflet	II/41	II	25.04.03	28.07.03
Extension of shelf-life or retest period of the active substance	I/42	I	21.03.03	01.04.03
Change in or addition of manufacturer(s) of active substance	I/43	I	23.04.03	29.04.03
Minor change of manufacturing process of the active substance	I/44	I	11.06.03	17.06.03

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **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; **X** refers to an Annex II application.
T refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.
N refers to a notification in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992.

[2] For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.

Minor change of manufacturing process of the active substance	I/45	I	12.06.03	17.06.03
Change or addition of a new pharmaceutical form	X/46	X	22.10.03	02.03.04
Change in supplier of an intermediate compound used in manufacture of the active substance	I/47	I	31.10.03	12.11.03
Minor change in the manufacturing process of the active substance	I/48	I	10.11.03	-
Change in BR/QC testing - repl./add. of batch control/testing site and replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	IB/49	IB	23.12.03	-
Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. Site	IB/50	IB	14.04.04	-
Update of Summary of Product Characteristics, Labelling and Package Leaflet	II/51	II	03.06.04	02.08.04
Minor change in the manufacturing process of the active substance	IB/52	IB	01.07.04	-
Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	IA/53	IA	30.06.04	-
Replacement/add. of manufacturing site: Secondary packaging site and Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	IA/54	IA	30.06.04	-
Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. Site	IB/55	IB	28.07.04	-
Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. Site	IB/56	IB	29.07.04	-
Minor change in the manufacturing process of the active substance	IB/57	IB	10.08.04	-