## STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

**For procedures finalised after 1 August 2003 please refer to module 8B.**

On the 9 March 2000 the Marketing Authorisation Holder applied for the change of the trade name from Alfatronol to Intron A. The MAH submitted a plan for switching to the centralised approved name Intron A, as part of the follow up measures requested by the CPMP.

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 to bring the package leaflet in line with the text of the SPC regarding the dose for the melanoma induction therapy and the in-use storage conditions | 0002 | II | 13.04.00 | 28.08.00 |
| Minor change of manufacturing process of active substance | 0003 | I/II | 25.05.00 | N/A |
| New purification process for the interferon alfa-2-b | 0004 | II | 27.07.00 | N/A |
| Change in pack size for a medicinal product | 0005 | I | 14.04.00 | N/A |
| Change in test procedures of the medicinal product | 0006 | I | 23.06.00 | N/A |
| Change in the batch size of finished product | 0007 | I/II | 27.07.00 | 28.08.00 |
| Minor changes in manufacture of the medicinal product | 0008 | I/II | 27.07.00 | 28.08.00 |
| Change in specifications of active substance | 0009 | I | 19.12.00 | N/A |
| Change in specifications of active substance | 0010 | I | 19.12.00 | N/A |
| Change in specifications of active substance | 0011 | I | 19.10.00 | N/A |
| Change in specifications of active substance | 0012 | I | 19.10.00 | N/A |
| Change in specifications of active substance | 0013 | I | 19.12.00 | N/A |
| Change in test procedure of active substance | 0014 | I | 19.20.00 | N/A |
| Change in or addition of manufacturing site(s) for part or all of the manufacturing site | 0015 | I | 15.11.00 | N/A |
| Change in test procedure of active substance | 0016 | I | 04.01.01 | N/A |
| Quality changes | 0017 | II | 20.09.01 | 15.10.01 |
| Change in the batch size of finished product | 0018 | I | 29.03.01 | N/A |
| Extension of shelf-life or retest period of the active substance | 0020 | I | 01.06.01 | N/A |
| Update the Summary of Product Characteristics (sections 4.4, 4.8) to include the adverse reactions: hypertriglyceridaemia and sarcoidosis as requested by the CPMP following the assessments of the second PSURs for Intron A and PegIntron; and to update corresponding text in the Package Leaflet. The Package Leaflet was also harmonised with the SPC with respect to the warning on aplastic anaemia. In addition, changes were made to contact details of the local representatives in the Package Leaflet. | 0021 | II | 17.01.01 | 19.04.02 |
| Increase the shelf-life of interferon alfa-2b, manufactured using the isoform conversion purification process, to 24 months | 0022 | I | 28.02.02 | N/A |
| Tighten the E.coli protein release specification for Interferon alfa-2b drug substance manufactured using the Isoform Conversion Process. The company has proposed to tighten the current release specification from 0.02% of total protein to less than or equal to 0.01% of total protein. | 0023 | I | 26.03.02 | N/A |

[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.

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|---|---|---|---|---|
| To include the following two changes to the release and stability specifications for interferon alfa-2b drug substance:<br>- Reverse phase HPLC purity test: introduction of release and stability specifications<br>- SDS-PAGE: change of reducing and non reducing release and stability specifications | 0024 | II | 25.07.02 | N/A |
| Increase the retention time window for the integration of impurity peaks in the IntronA Solution for Injection Vials RP-HPLC purity test. | 0025 | I | 13.08.02 | N/A |
| Update the SPC (sections 4.4, 4.8), to reinforce the warning and safety information with regard to ophthalmic disorders. A corresponding warning in the Package leaflet was also requested. Section 4.8 was also modified to indicate that reactions could occur with Intron A monotherapy as well as with combination therapy. | 0026 | II | 19.09.02 | 05.12.02 |
| Extend the currently approved in-use shelf-life from 12 days with a total of 6 injections (3 times a week) to 27 days with a total of 12 injections (3 times a week). As a consequence, the number of needles and swaps provided per pen must be doubled and new pack sizes are proposed as a consequential variation. | 0027 | I | 28.08.02 | 10.10.02 |
| Update of the flow-charts of the secondary packaging sites. | 0028 | I | 10.09.02 | 10.09.02 |
| Replacement of RAU-SIK silicone tubing by RAUMEDIC-PLATIN-SIK silicone tubing for filling IntronA powder for Injection batches in Operations 1, Building 4 of the manufacturing facility in Brinny (Ireland). | 0029 | I/II | 17.10.02 | N/A |
| Replace the current Polysorbate 80 from animal origin used as an excipient for the drug product by Polysorbate 80 from vegetable origin. | 0030 | I | 22.11.02 | N/A |
| Applied for an additional supplier of HSA (Instituto Grifols S.A., Barcelona, Spain). The Marketing Authorisation Holder took the opportunity to change the pharmacopoeial reference to Ph. Eur. for Dibasic Sodium Phosphate Anhydrous. | 0031 | II | 19.03.03 | N/A |
| Update of section 4.4 of the SPC to reinforce the warning on auto-immune disorders and to add a warning regarding HCV/HIV co-infected patients. A statement on the use of paracetamol was removed.<br>Section 4.8 was updated to add the adverse events: Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Information on auto-immune and immune mediated disorders was also added. The MAH took the opportunity to bring section 4.8 into line with current guidelines with the consequential change of section 4.8 to a tabular format with the addition of adverse reactions occurring at the 1% level.<br>A warning regarding the teratogenicity and embryocidicity of ribavirin was added to section 4.6 since the recommended use of Intron A in the treatment of hepatitis C is in combination with ribavirin.<br>The term “histologically proven” was deleted from 4.1 and a cross reference to a new warning in 4.4 inserted.<br>Minor changes to section 4.2 were requested to remove a discrepancy between two statements.<br>Corresponding changes were made to the Package Leaflet. | 0032 | II | 25.04.03 | 28.07.03 |
| Introduction of a low control limit (in addition to the existing high control limit) for the quantitiy of TCA precipitate used in the TCA precipitate extraction step of the interferon alfa-2b active substance purification process. | 0033 | I/II | 26.06.03 | N/A |