IntronA

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
IB/0122	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/06/2021		SmPC, Annex II, Labelling and PL	
N/0121	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2019	15/10/2020	Labelling and PL	

[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).

IB/0120	C.I.7.a - Deletion of - a pharmaceutical form	22/10/2019	15/10/2020	SmPC, Labelling and PL	
IB/0119	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	13/06/2019	n/a		
IG/1088	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	05/04/2019	n/a		
N/0117	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2019	15/10/2020	Labelling	
T/0116	Transfer of Marketing Authorisation	17/07/2018	28/09/2018	SmPC, Labelling and PL	
IB/0115/G	This was an application for a group of variations. B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	18/05/2018	n/a		

IG/0884	A.7 - Administrative change - Deletion of manufacturing sites	21/12/2017	n/a		
PSUSA/1758/ 201609	Periodic Safety Update EU Single assessment - interferon alpha-2b	22/06/2017	28/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1758/201609.
WS/1216	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/09/2017	n/a		
IG/0834	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	29/08/2017	n/a		
WS/1105	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on HCV/HBV co-infection and to add hepatitis B reactivation in HCV/HBV co-infected patients as an ADR, respectively, based on post marketing adverse experience. The Labelling and Package Leaflet are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD	22/06/2017	28/09/2017	SmPC, Annex II, Labelling and PL	Cases of hepatitis B re-activation (some with severe consequences) have been reported in patients co-infected with hepatitis B and C viruses treated with interferon. The frequency of such re-activation appears to be low. All patients should be screened for hepatitis B before starting treatment with interferon for hepatitis C; patients co-infected with hepatitis B and C must then be monitored and managed according to current clinical guidelines.

	template version 10 including the implementation of the use of combined SmPCs and PLs for PegIntron and ViraferonPeg and the use of combined SmPCs for Intron A in multidose pen. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0110	Update of section 4.8 of the SmPC in order to add pericarditis with the frequency uncommon based on continuous monitoring of the safety profile; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/06/2017	28/09/2017	SmPC and PL	
IA/0111	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	28/04/2017	n/a		
IG/0763/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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	06/02/2017	22/05/2017	Annex II	

	(excluding manufacturer for batch release)				
IB/0106/G	This was an application for a group of variations. 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 B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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 B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within	15/12/2015	22/05/2017	SmPC, Labelling and PL	

					children and adolescents experienced other psychiatric adverse events (e.g., depression, emotional lability, and somnolence). Other CNS effects including aggressive behaviour (sometimes directed against others), confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with IntronA be discontinued, and the patient followed, with psychiatric intervention as appropria
II/0044	Update of or change(s) to the pharmaceutical documentation	15/09/2005	23/09/2005		
IB/0046	IB_20_c_Change in test procedure for an excipient - other changes	13/09/2005	n/a		
IA/0047	IA_28_Change in any part of primary packaging material not in contact with finished product	31/08/2005	n/a		
R/0041	Renewal of the marketing authorisation.	17/02/2005	23/05/2005	SmPC, Annex II, Labelling and PL	The CHMP was of the opinion that the quality, safety and efficacy of IntronA continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of this medicinal product remains favourable.
II/0040	Change(s) to the manufacturing process for the	20/01/2005	31/01/2005		

	finished product				
II/0034	Extension of Indication	21/10/2004	25/01/2005	SmPC and PL	Chidren and adolescents with Chronic Hepatitis C: IntronA is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighed against the safety findings observed for paediatric subjects in the clinical trials. Interferon alfa-2b 3 MIU/m2 is administered subcutaneously 3 times a week (every other day) in combination with ribavirin capsules or solution administered orally in two divided doses daily with food (morning and evening). (See ribavirin capsule SPC for dose of ribavirin capsules and dosage modification guidelines for combination therapy. For paediatric patients who weigh < 47 kg or cannot swallow capsules, see ribavirin oral solution SPC). Clinical trials in paediatric patients with chronic hepatitis C: Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based

					RT-PCR assay) were enrolled in two multicentre trials and received IntronA 3 MIU/m2 3 times a week plus ribavirin 15 mg/kg per day for 1 year followed by 6 months follow-up after-treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1, 64 % £ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. Sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of t
IA/0043	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/12/2004	n/a		
IA/0042	IA_09_Deletion of manufacturing site	08/12/2004	n/a		
II/0036	Update of or change(s) to the pharmaceutical documentation	16/09/2004	28/10/2004	SmPC and PL	The MAH applied for an update of the Plasma Master File. In the context of this update, the MAH took the opportunity to amend the SPC and PL to comply with the "Note for Guidance on the warning on transmissable agents in SPCs and PLs for plasma-derived products (CPMP/BPWG/BWP/561/03)".
II/0039	Update of Summary of Product Characteristics, Labelling and Package Leaflet	29/07/2004	13/09/2004	SmPC, Labelling and PL	The MAH applied to modify the safety information in the SPC of Intron A with the following: -Addition of ischaemia and cerebrovascular haemorrhage in section 4.8 as requested by the CHMP following the assessment of a Follow-Up Measure concerning cerebral haemorrhage. -Addition of encephalopathy in section 4.4 and 4.8, hearing loss in section 4.8 and modification of the section regarding

					cardiac disorders in section 4.8 as requested by CHMP. -Addition of myosisits, colitis and injection site necrosis in section 4.8 and modifications of the warning on graft rejection in section 4.4 as a harmonisation with peginterferon alfa. During this procedure the CHMP recommended to replace the existing contraindication in patients with existence of or history of severe psychiatric conditions by a warning in section 4.4. The PL has been updated accordingly. The MAH took this opportunity to include editorial changes and update the wording of the storage conditions in the SPC, PL and labelling in accordance with the latest templates. Additional minor changes were made to the SPC and PL, mainly sections 3 and 6.6, regarding the need for a colourless solution.
II/0038	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	02/08/2004		
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/05/2004	n/a	PL	
I/0035	20a_Extension of shelf-life or retest period of the active substance	06/11/2003	13/11/2003		
II/0032	Update of or change(s) to the pharmaceutical documentation Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	28/07/2003	SmPC and PL	

I/0033	12_Minor change of manufacturing process of the active substance	26/06/2003	14/07/2003		
II/0031	Quality changes	19/03/2003	31/03/2003		
II/0026	Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	05/12/2002	SmPC and PL	
I/0030	04_Replacement of an excipient with a comparable excipient	22/11/2002	03/12/2002		
I/0029	15_Minor changes in manufacture of the medicinal product	17/10/2002	28/10/2002		
I/0027	21_Change in shelf-life after first opening 30_Change in pack size for a medicinal product	28/08/2002	10/10/2002	SmPC, Labelling and PL	
I/0028	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/09/2002	24/09/2002		
I/0025	25_Change in test procedures of the medicinal product	13/08/2002	17/09/2002		
II/0024	Change(s) to the test method(s) and/or specifications for the active substance	25/07/2002	30/07/2002		
II/0021	Update of Summary of Product Characteristics and Package Leaflet	17/01/2002	19/04/2002	SmPC and PL	
I/0023	14_Change in specifications of active substance	26/03/2002	08/04/2002		

II/0019	Update of Summary of Product Characteristics and Package Leaflet	18/10/2001	02/04/2002	SmPC and PL	
I/0022	20a_Extension of shelf-life or retest period of the active substance	28/02/2002	06/03/2002		
II/0017	Update of or change(s) to the pharmaceutical documentation	20/09/2001	12/10/2001		
I/0018	16_Change in the batch size of finished product	29/03/2001	21/05/2001		
I/0016	24_Change in test procedure of active substance	04/01/2001	21/05/2001		
I/0014	24_Change in test procedure of active substance	19/12/2000	21/05/2001		
I/0013	14_Change in specifications of active substance	19/12/2000	21/05/2001		
I/0012	14_Change in specifications of active substance	19/10/2000	21/05/2001		
I/0011	14_Change in specifications of active substance	19/10/2000	21/05/2001		
I/0010	14_Change in specifications of active substance	19/12/2000	21/05/2001		
I/0009	14_Change in specifications of active substance	19/12/2000	21/05/2001		
I/0015	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	15/11/2000	15/11/2000		
II/0002	Update of Summary of Product Characteristics and Package Leaflet	13/04/2000	28/08/2000	PL	

I/0008	15_Minor changes in manufacture of the medicinal product	27/07/2000	28/08/2000		
I/0007	16_Change in the batch size of finished product	27/07/2000	28/08/2000		
I/0006	25_Change in test procedures of the medicinal product	23/06/2000	28/08/2000		
I/0005	30_Change in pack size for a medicinal product	14/04/2000	21/08/2000		
II/0004	Change(s) to the manufacturing process for the active substance	27/07/2000	01/08/2000		
I/0003	12_Minor change of manufacturing process of the active substance	25/05/2000	n/a		
I/0001	02_Change in the name of the medicinal product (either invented name of common name)	10/03/2000	17/05/2000	SmPC, Labelling and PL	