Aprovel

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
A31/0172	The European Commission triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of nitrosamine impurities on the benefit-risk balance of valsartan-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. During the CHMP plenary meeting in September 2018, the scope of the referral has been widened to include	31/01/2019	11/04/2019	Annex II	Please refer to the assessment report: Aprovel EMEA/H/A-31/1471/C/141/0172

[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).

	all sartans with a tetrazole group in their molecular structure (candesartan, irbesartan, losartan, olmesartan and valsartan).				
IG/1065	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	28/03/2019	n/a		
IG/1027	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	05/12/2018	n/a		
IB/0171/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	27/07/2018	n/a		
WS/1346	This was an application for a variation following a worksharing procedure according to Article 20 of	26/07/2018	11/04/2019	SmPC, Labelling and	

	Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add 'anaphylactic reaction including anaphylactic shock' to the list of adverse drug reactions. The PL is updated accordingly. In addition, the MAH took the opportunity to update the information on local representatives in Bulgaria and Germany and to update the product information in line with the latest QRD template (version 10). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			PL	
IB/0169/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	02/08/2017	30/07/2018	Annex II and PL	

IG/0814	A.7 - Administrative change - Deletion of manufacturing sites	28/07/2017	n/a		
IB/0167	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	25/07/2017	n/a		
IB/0166/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 B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	02/06/2017	n/a		
IB/0165/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	05/01/2017	n/a		

PSUSA/1782/ 201508	Periodic Safety Update EU Single assessment - irbesartan	28/04/2016	24/06/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1782/201508.
N/0163	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2015	24/06/2016	PL	
N/0162	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2015	24/06/2016	PL	
IB/0161	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	19/02/2015	n/a		
A31/0154	On 17 April 2013, further to the emergence of new evidence from the scientific literature on dual RAS blockade therapy and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) initiated a review under Article 31 of Council Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the combined use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs) or aliskiren and to determine whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure.	22/05/2014	04/09/2014	SmPC and PL	For further information please refer to the Renin-angiotensin-system (RAS)-acting agents Article 31 referral- Assessment report.

IG/0454	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	17/07/2014	n/a		
IA/0159	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	14/05/2014	n/a		
N/0158	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2014	04/09/2014	PL	
IG/0331	A.1 - Administrative change - Change in the name and/or address of the MAH	04/10/2013	04/09/2014	SmPC, Labelling and PL	
IA/0156	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	26/09/2013	n/a		
IG/0327	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/08/2013	n/a		
II/0148	Update of SmPC sections 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor Blockers (ARBs) with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus. The Package Leaflet has been	27/06/2013	31/07/2013	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion "Aprovel-EMEA-H-C-0141-II-148".

	updated accordingly. In addition, the MAH took the opportunity to align the annexes with the latest QRD template, to make editorial changes in the annexes and to introduce the contact details of the local representative in Croatia in the Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
IA/0153	A.7 - Administrative change - Deletion of manufacturing sites	05/06/2013	31/07/2013	Annex II and PL	
IB/0151	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	06/05/2013	n/a		
IA/0152	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	26/04/2013	n/a		
II/0149	Change in the specifications limits range for the active substance Irbesartan. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	25/04/2013	n/a		

IA/0150	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	22/04/2013	n/a		
IAIN/0147	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/01/2013	n/a		
IA/0146	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2012	n/a		
IA/0145	B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	09/11/2012	n/a		
IB/0144/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the 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	15/10/2012	n/a		
IA/0143	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	26/07/2012	10/10/2012	SmPC	

IAIN/0142	A.1 - Administrative change - Change in the name and/or address of the MAH	03/04/2012	10/10/2012	SmPC, Labelling and PL	
IA/0141	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/02/2012	n/a		
IB/0139	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	10/01/2012	n/a		
IB/0138	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	10/01/2012	n/a		
IB/0140	B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation	04/01/2012	n/a		
II/0132	Update of the Summary of Product Characteristics. Update of SmPC sections 4.6 and 5.3 with wording related to fertility. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	17/06/2011	SmPC	It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk. Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (from 50 to 650 mg/kg/day), including mortality at the highest dose. No significant effects on the number of corpora lutea, implants, or live fetuses were observed. Irbesartan did not affect survival, development, or reproduction of offspring. Studies in animals indicate that the radiolabeled irbesartan is detected in rat and rabbit fetuses.

IA/0137	A.7 - Administrative change - Deletion of manufacturing sites	27/05/2011	n/a		
WS/0074	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics and Package Leaflet C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	14/04/2011	23/05/2011	SmPC and PL	This type IB variation concerns an update of section 4.8 of the SmPC with the ADR 'jaundice', upon request by the CHMP following the assessment of irbesartan PSUR 15 and FU2 020.1. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC and Package Leaflet. This application was submitted following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
IA/0136	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/05/2011	n/a		
IA/0133/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	08/04/2011	n/a		

IB/0135	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	06/04/2011	n/a		
IA/0134	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	22/03/2011	n/a	Annex II	
II/0126	This type II variation concerns an update of section 4.8 of the SPC, upon request by the CHMP following the assessment of the irbesartan PSUR covering 12 Aug 2006 - 11 Aug 2009, to add the ADR "Vertigo" with the frequency of "not known" under 'post-marketing experience'. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to align the product information with the latest QRD template (version 7.3) and the Guideline on Summary of Product Characteristics (September 2009). C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/09/2010	28/10/2010	SmPC and PL	
IA/0131/G	This was an application for a group of variations.	28/10/2010	n/a	Annex II	

	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 C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV				
IB/0130	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/08/2010	n/a		
IA/0129	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	06/07/2010	n/a		
IB/0128	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	10/06/2010	n/a		
IB/0127	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	19/05/2010	n/a		
N/0125	To change the phone number of the Slovak local representative in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/03/2010	n/a	PL	

IA/0124/G	This was an application for a group of variations. 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	22/03/2010	n/a	Annex II	
IB/0123	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	02/12/2009	n/a		
II/0122	Change of the manufacturing site of irbesartan and as a consequence a change in the batch size of this active substance. Change(s) to the manufacturing process for the active substance	24/09/2009	07/10/2009		
IA/0121	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/07/2009	n/a		
IA/0120	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/06/2009	n/a		
N/0119	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2009	n/a	PL	
IA/0118	IA_32_a_Change in batch size of the finished product - up to 10-fold	27/04/2009	n/a		

IB/0117	IB_10_Minor change in the manufacturing process of the active substance	17/04/2009	n/a		
II/0116	The MAH applied for an update of the SPC sections 4.3 and 4.6 as well as PL section 2 to implement the CHMP recommendation on a harmonised labelling relating to the use of Angiotensin II Receptor Antagonists during pregnancy and lactation. Furthermore, minor typographical changes have been introduced to SPC section 4.4. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	31/03/2009	SmPC and PL	Available data regarding use of AIIRAs during lactation have been assessed. There are no concrete data to support the contraindication of use of AIIRAs during breast-feeding. All AIIRA agents were found in the milk of lactating rats but no human data about their transfer into breast milk are available. There is only a theoretical presumption of low transport according to their high plasma protein binding and low oral availability. A harmonised wording recommending an alternative treatment with better established safety profiles during breast-feeding, especially while nursing a newborn or preterm infant, has been included in the section 4.6 of the SPC and section 2 of the PL. Consequently, the existing contraindication for lactation has been deleted.
II/0115	Update of Detailed Description of the Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	26/02/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 3.0) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
IB/0114	IB_10_Minor change in the manufacturing process of the active substance IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/08/2008	n/a		
N/0112	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/08/2008	n/a	PL	

IA/0113	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/07/2008	n/a		
II/0109	Update of Summary of Product Characteristics and Package Leaflet The MAH applied for an update of the SPC sections 4.3, 4.4, and 4.6 as well as PL section 2 to implement the CHMP recommendation on a harmonised labelling relating to the use of ACE inhibitors and Angiotensin II Receptor Antagonists during pregnancy. In addition, linguistic corrections to the German, French, Latvian, Dutch and Romanian Package Leaflets were proposed Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	10/06/2008	SmPC, Labelling and PL	Cooper's study published in the NEJM in June 2006 identified a signal of increased risk of congenital malformations, particularly cardiac defects after exposure to ACE inhibitors during the first trimester of pregnancy. Since the role of confounding factors such as diabetes and hypertension cannot be accurately defined based on the available data, the teratogenic potential of ACE inhibitors is not demonstrated, even though data suggest that such exposure cannot be considered as safe and should be avoided. There are fewer data regarding the risks associated with first trimester exposure to Angiotensin II receptor antagonists (AIIRAs) than for ACE inhibitors. Nevertheless, there is no evidence that the risk is lower for AIIRAs, and it is considered that any conclusions on ACE inhibitors are also valid for AIIRAs. Therefore, the existing contraindication for the 2nd and 3rd trimester of pregnancy remained, but a harmonised wording regarding pregnancy across the class was introduced
IB/0111	IB_10_Minor change in the manufacturing process of the active substance IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	25/04/2008	n/a		
IA/0110	IA_09_Deletion of manufacturing site	03/04/2008	n/a		
IA/0108	IA_09_Deletion of manufacturing site	13/02/2008	n/a		

N/0106	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2007	n/a	PL	
IB/0105	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	20/12/2007	n/a	SmPC, Labelling and PL	
IA/0107	IA_09_Deletion of manufacturing site	13/12/2007	n/a		
IA/0104	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	27/09/2007	n/a		
IB/0103	IB_10_Minor change in the manufacturing process of the active substance	21/09/2007	n/a		
R/0093	Renewal of the marketing authorisation.	21/06/2007	31/08/2007	SmPC, Annex II, Labelling and PL	
IA/0102	IA_32_a_Change in batch size of the finished product - up to 10-fold	23/03/2007	n/a		
IA/0101	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	23/03/2007	n/a		
N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/03/2007	n/a	PL	
IA/0100	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
IA/0099	IA_41_a_01_Change in pack size - change in no. of	21/03/2007	21/03/2007	SmPC,	

	units within range of appr. pack size			Labelling and PL	
IA/0098	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
IA/0097	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
IA/0096	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
IA/0095	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
IA/0092	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/01/2007	n/a	Annex II and PL	
IA/0091	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	09/01/2007	n/a		
IA/0090	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	05/12/2006	n/a		
IB/0089	IB_10_Minor change in the manufacturing process of the active substance	29/11/2006	n/a		
IB/0088	IB_33_Minor change in the manufacture of the finished product IA_32_a_Change in batch size of the finished product	10/11/2006	n/a		

	- up to 10-fold				
IA/0087	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	11/09/2006	n/a		
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/09/2006	n/a	PL	
IA/0085	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	30/08/2006	n/a		
IB/0084	IB_10_Minor change in the manufacturing process of the active substance	21/08/2006	n/a		
IA/0083	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/07/2006	n/a		
IA/0082	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/07/2006	n/a		
IA/0081	IA_09_Deletion of manufacturing site	11/07/2006	n/a	Annex II and PL	
IB/0078	IB_10_Minor change in the manufacturing process of the active substance	28/06/2006	n/a		
IA/0080	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	22/06/2006	n/a		
IA/0079	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	20/06/2006	n/a		

II/0077	Update of Summary of Product Characteristics (4.8) following the evaluation of the 13th PSUR. Update of Summary of Product Characteristics	27/04/2006	31/05/2006	SmPC	At least 30 cases of renal failure have been identified in the last two PSURs. Therefore, the wording "isolated cases of renal failure" is no longer applicable. In addition, the frequency of "renal failure" and all other ADRs listed in the SPC detected from spontaneous reporting in the post-authorisation phase should be referred to as "not known" rather than "very rare" or "rare", in accordance to the SPC guideline.
II/0075	Update of Summary of Product Characteristics (sections 4.2, 4.8, 5.1 and 5.2) and Package Leaflet to reflect pharmacokinetic, pharmacodynamic and safety information in children and adolescents. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	31/05/2006	SmPC and PL	Please refer to the Scientific discussion: Aprovel-H-141-II-75.
IB/0076	IB_10_Minor change in the manufacturing process of the active substance	29/03/2006	n/a		
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/01/2006	n/a	PL	
IB/0073	IB_10_Minor change in the manufacturing process of the active substance	16/01/2006	n/a		
II/0068	Update of Summary of Product Characteristics, Labelling and Package Leaflet following a PSUR Assessment Report and the implementation of new QRD templates.	17/11/2005	09/01/2006	SmPC, Labelling and PL	Addition of the ADRs leukocytoclastic vasculitis and muscle cramp, and of a statement reflecting the observation that increased plasma creatine kinase may be associated with musculoskeletal events.

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				
IB/0072	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/11/2005	n/a		
IB/0071	IB_10_Minor change in the manufacturing process of the active substance	15/11/2005	n/a		
IA/0070	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	28/09/2005	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/09/2005	n/a	PL	
IB/0065	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	16/09/2005	n/a		
IA/0067	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	15/09/2005	n/a		
IA/0066	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/09/2005	n/a	Annex II and PL	
IB/0063	IB_10_Minor change in the manufacturing process of the active substance	01/09/2005	n/a		
IA/0064	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	18/08/2005	18/08/2005	SmPC, Labelling and PL	
IA/0062	IA_11_b_Change in batch size of active substance or	03/08/2005	n/a		

	intermediate - downscaling				
IB/0061	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	11/04/2005	n/a	Annex II and PL	
IA/0060	IA_05_Change in the name and/or address of a manufacturer of the finished product	10/02/2005	n/a	Annex II, Labelling and PL	
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/11/2004	n/a	PL	
IA/0058	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/09/2004	n/a		
IB/0057	IB_10_Minor change in the manufacturing process of the active substance	10/08/2004	n/a		
II/0051	Update of Summary of Product Characteristics, Labelling and Package Leaflet	03/06/2004	02/08/2004	SmPC, Labelling and PL	
IB/0056	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	29/07/2004	n/a		
IB/0055	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	28/07/2004	n/a		

IB/0052	IB_10_Minor change in the manufacturing process of the active substance	01/07/2004	n/a		
IA/0054	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	30/06/2004	n/a	Annex II and PL	
IA/0053	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	30/06/2004	n/a	Annex II and PL	
IB/0050	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	14/04/2004	n/a		
X/0046	X-3-iv_Change or addition of a new pharmaceutical form	22/10/2003	02/03/2004	SmPC, Annex II, Labelling and PL	
IB/0049	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	23/12/2003	n/a		
I/0047	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	31/10/2003	12/11/2003		
I/0048	IB_10_Minor change in the manufacturing process of the active substance	10/11/2003	n/a		
II/0041	Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	28/07/2003	SmPC and PL	

I/0045	12_Minor change of manufacturing process of the active substance	12/06/2003	17/06/2003		
I/0044	12_Minor change of manufacturing process of the active substance	11/06/2003	17/06/2003		
I/0043	11_Change in or addition of manufacturer(s) of active substance	23/04/2003	29/04/2003		
I/0042	20a_Extension of shelf-life or retest period of the active substance	21/03/2003	01/04/2003		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2003	07/03/2003	PL	
I/0039	12_Minor change of manufacturing process of the active substance	19/12/2002	17/01/2003		
R/0037	Renewal of the marketing authorisation.	25/07/2002	29/10/2002	SmPC, Annex II, Labelling and PL	
I/0038	15_Minor changes in manufacture of the medicinal product	05/06/2002	18/06/2002		
II/0029	Extension of Indication	21/02/2002	12/06/2002	SmPC and PL	
I/0036	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	10/04/2002	30/04/2002		

II/0023	Update of Summary of Product Characteristics and Package Leaflet	20/09/2001	10/04/2002	SmPC and PL	
I/0035	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	10/04/2002	10/04/2002		
I/0034	01_Change following modification(s) of the manufacturing authorisation(s)	22/12/2001	08/03/2002	Annex II and PL	
I/0031	04_Replacement of an excipient with a comparable excipient	22/10/2001	27/02/2002		
I/0033	16_Change in the batch size of finished product	26/11/2001	19/02/2002		
I/0030	30_Change in pack size for a medicinal product	20/09/2001	19/02/2002	SmPC, Labelling and PL	
I/0028	30_Change in pack size for a medicinal product	20/09/2001	19/02/2002	SmPC, Labelling and PL	
I/0027	30_Change in pack size for a medicinal product	20/09/2001	19/02/2002	SmPC, Labelling and PL	
I/0032	01_Change following modification(s) of the manufacturing authorisation(s)	11/01/2002	n/a	Annex II and PL	
I/0026	30_Change in pack size for a medicinal product	13/07/2001	08/10/2001	SmPC, Labelling and PL	

I/0025	30_Change in pack size for a medicinal product	13/07/2001	08/10/2001	SmPC, Labelling and PL	
I/0024	30_Change in pack size for a medicinal product	13/07/2001	08/10/2001	SmPC, Labelling and PL	
I/0022	12_Minor change of manufacturing process of the active substance	26/04/2001	n/a		
I/0021	26_Changes to comply with supplements to pharmacopoeias	20/03/2001	n/a		
I/0018	20_Extension of shelf-life as foreseen at time of authorisation	26/10/2000	15/01/2001	SmPC	
II/0017	Update of Summary of Product Characteristics and Package Leaflet	27/07/2000	14/11/2000	SmPC and PL	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	16/12/1999	25/04/2000	SmPC, Annex II, Labelling and PL	
I/0016	12_Minor change of manufacturing process of the active substance	21/12/1999	n/a		
I/0014	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	08/09/1999	22/09/1999		
I/0013	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	01/06/1999	n/a		

I/0012	01_Change following modification(s) of the manufacturing authorisation(s)	28/04/1999	n/a	PL	
II/0008	Update of Summary of Product Characteristics and Package Leaflet	16/12/1998	13/04/1999	SmPC, Annex II and PL	
I/0010	03_Change in the name and/or address of the marketing authorisation holder	05/11/1998	23/02/1999	SmPC, Labelling and PL	
I/0011	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/01/1999	n/a		
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/1998	13/04/1999	Labelling	
I/0007	15_Minor changes in manufacture of the medicinal product	23/10/1998	n/a		
I/0006	11_Change in or addition of manufacturer(s) of active substance	07/08/1998	n/a		
I/0005	12_Minor change of manufacturing process of the active substance	20/02/1998	n/a		
I/0004	11_Change in or addition of manufacturer(s) of active substance	17/10/1997	n/a		
I/0003	16_Change in the batch size of finished product	04/09/1997	n/a		
I/0002	11_Change in or addition of manufacturer(s) of active	04/09/1997	n/a		

	substance				
I/0001	11_Change in or addition of manufacturer(s) of active substance	04/09/1997	n/a		