Karvea

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
N/0198	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/08/2024		PL	
IA/0197	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	18/06/2024	n/a		

[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).

	from an already approved manufacturer				
N/0196	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/07/2023		PL	
T/0195	Transfer of Marketing Authorisation Transfer of Marketing Authorisation	05/12/2022	16/12/2022	SmPC, Labelling and PL	
IG/1557	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	11/10/2022	16/12/2022	Annex II	To update Annex II in line with the outcome of the Article 31 referral on angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471) and Article 5(3) assessment on nitrosamines (EMEA/H/A-5(3)/1490).
IG/1509	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	17/06/2022	n/a		
PSUSA/10601 /202108	Periodic Safety Update EU Single assessment - irbesartan, irbesartan / hydrochlorothiazide	07/04/2022	n/a		PRAC Recommendation - maintenance
WS/2213/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	31/03/2022	n/a		

	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				
IG/1451	A.7 - Administrative change - Deletion of manufacturing sites	15/02/2022	13/09/2022	Annex II and PL	
WS/2180	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	02/12/2021	n/a		
WS/2172	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	25/11/2021	n/a		
WS/2122	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the	23/09/2021	13/09/2022	Annex II	Update of Annex II of the product information and lifting of condition D.

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IG/1378	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	20/04/2021	n/a		
WS/1969	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add anemia to the list of adverse drug reactions with frequency unknown based on a review of the available data including the MAH database and a literature review; 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	25/03/2021	10/05/2021	SmPC and PL	
A31/0175	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	12/11/2020	12/02/2021	Annex II	Please refer to the assessment report: Karvea EMEA/H/A-31/1471/C/142/0175

	include all sartans with a tetrazole group in their molecular structure (candesartan, irbesartan, losartan, olmesartan and valsartan). The CHMP Opinion was issued on 31 January 2019 and the Commission Decision was issued on 2 April 2019. In a letter dated 29 July 2020, the European Commission requested the EMA to assess the impact of the outcome of the Article 5(3) assessment on nitrosamines adopted on 25 June 2020 on the CHMP's opinion of 31 January 2019 for the scientific assessment and review under Article 31 of Directive 2001/83/EC regarding angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H/A-31/1471). The CHMP was requested to give its recommendation whether the conditions of the Marketing Authorisations should be varied.				
WS/1886/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Group of variations consisting of: C.I.4 - Update of section 4.4 and 4.8 of the SmPC to add information on hypoglycaemia based on a review of available data including the MAH pharmacovigilance data base and a literature review. The Package leaflet is updated accordingly. C.I.4 - Update of 4.4 and 4.5 of the SmPC to add	14/01/2021	10/05/2021	SmPC and PL	Based on a review of the available data including the MAH database and a literature review information was added to the SmPC to inform that irbesartan may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated. Hypoglycaemia has been added as an undesirable effect under frequency not known. Irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the Cmax and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3 fold, respectively, when administered 1

	information on a drug -drug interaction with irbesartan and repaglinide based on a review of the available data including the MAH database and a literature review. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement the updated annex to the European Commission guideline on Excipients in the labelling and package leaflet of medicinal products for human use' to update the excipient sodium. The MAH also took the opportunity to update the list of local representatives in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required. The product leaflet is updated accordingly. For more information, please refer to the Summary of Product Characteristics.
IG/1272	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)	23/07/2020	n/a		
IB/0181/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where	07/05/2020	10/05/2021	Annex II	

	batch control/testing takes place B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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) 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) 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) 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) 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 B.III.2.b - Change to comply with Ph. Eur. or with a				

	national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
IG/1220/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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	27/03/2020	n/a		
N/0180	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/02/2020	10/05/2021	PL	
IG/1187	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	19/12/2019	n/a		
IB/0178/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	14/10/2019	n/a		

	increase compared to the originally approved batch size				
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		
WS/1346	This was an application for a variation following a worksharing procedure according to Article 20 of 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	26/07/2018	02/04/2019	SmPC, Labelling and PL	
IB/0173/G	This was an application for a group of variations.	02/08/2017	13/07/2018	Annex II and	

	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			PL	
IG/0814	A.7 - Administrative change - Deletion of manufacturing sites	28/07/2017	n/a		
IB/0171	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/0170/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	02/06/2017	n/a		

	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				
IB/0169/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	21/06/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1782/201508.
N/0167	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2015	21/06/2016	PL	
N/0166	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2015	21/06/2016	PL	
IB/0165	B.I.b.2.e - Change in test procedure for AS or	19/02/2015	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
A31/0159	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/0163	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	14/05/2014	n/a		

	an obsolete parameter)				
N/0162	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2014	04/09/2014	PL	
IA/0161	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/0153	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 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	27/06/2013	31/07/2013	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion "Karvea-EMEA-H-C-0142-II-153".
IA/0158	A.7 - Administrative change - Deletion of manufacturing sites	05/06/2013	31/07/2013	Annex II and	

				PL	
IB/0156	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/0157	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/0154	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/0155	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		
T/0152	Transfer of Marketing Authorisation	01/02/2013	18/02/2013	SmPC, Labelling and PL	
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0150	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2012	n/a		

IA/0149	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/0148/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/0147	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	
IA/0146	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/02/2012	n/a		
IB/0144	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	13/01/2012	n/a		

IB/0143	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	11/01/2012	n/a		
IB/0145	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/0136	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	29/06/2011	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/0141	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	14/04/2011	18/05/2011	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.

	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				This application was submitted following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
IA/0140	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/0137/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/0139	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/0138	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	29/03/2011	n/a	Annex II	

IA/0135/G	This was an application for a group of variations. 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	28/10/2010	n/a	Annex II	
II/0130	Update of Summary of Product Characteristics and 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	23/09/2010	25/10/2010	SmPC and PL	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).
IB/0134	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/0133	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/0132	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an	10/06/2010	n/a		

	ASMF				
IB/0131	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/0129	To update the contact details of the local representatives in the Package Leaflet for Belgium, Luxembourg, Estonia and Cyprus. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/03/2010	n/a	PL	
IA/0128/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/0127	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	02/12/2009	n/a		
II/0126	Change of the manufacturing site of irbesartan and as a consequence a change in the batch size of this active substance.	24/09/2009	05/10/2009		

	Change(s) to the manufacturing process for the active substance				
IA/0125	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/07/2009	n/a		
IA/0124	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/06/2009	n/a		
IA/0123	IA_32_a_Change in batch size of the finished product - up to 10-fold	27/04/2009	n/a		
IB/0122	IB_10_Minor change in the manufacturing process of the active substance	17/04/2009	n/a		
II/0121	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/0120	Update of Detailed Description of the	22/01/2009	26/02/2009	Annex II	The Detailed Description of the Pharmacovigilance System

	Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)				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/0119	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/0117	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/08/2008	n/a	PL	
IA/0118	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/07/2008	n/a		
II/0114	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. 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/0116	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/0115	IA_09_Deletion of manufacturing site	03/04/2008	n/a		
IA/0113	IA_09_Deletion of manufacturing site	13/02/2008	n/a		
N/0111	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2007	n/a	PL	
IB/0110	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product	20/12/2007	n/a	SmPC, Labelling and PL	
IA/0112	IA_09_Deletion of manufacturing site	13/12/2007	n/a		
IA/0109	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	27/09/2007	n/a		
IB/0108	IB_10_Minor change in the manufacturing process of the active substance	21/09/2007	n/a		
R/0098	Renewal of the marketing authorisation.	21/06/2007	31/08/2007	SmPC, Annex II, Labelling	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance,

				and PL	the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Aprovel continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
N/0107	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/06/2007	n/a	PL	
IA/0106	IA_32_a_Change in batch size of the finished product - up to 10-fold	23/03/2007	n/a		
IA/0105	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	23/03/2007	n/a		
IA/0104	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/0103	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/0102	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/0101	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/0100	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/0099	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_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/0096	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	09/01/2007	n/a		
IA/0095	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/0093	IB_10_Minor change in the manufacturing process of the active substance	29/11/2006	n/a		
N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2006	n/a	PL	
IB/0092	IB_33_Minor change in the manufacture of the finished product IA_32_a_Change in batch size of the finished product - up to 10-fold	10/11/2006	n/a		
IA/0091	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	11/09/2006	n/a		
IA/0090	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/0089	IB_10_Minor change in the manufacturing process of the active substance	21/08/2006	n/a		
IA/0088	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/07/2006	n/a		
IA/0087	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/07/2006	n/a		
IA/0086	IA_09_Deletion of manufacturing site	11/07/2006	n/a	Annex II and PL	
IB/0083	IB_10_Minor change in the manufacturing process of the active substance	28/06/2006	n/a		
IA/0085	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	22/06/2006	n/a		
IA/0084	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	20/06/2006	n/a		
II/0082	Update of Summary of Product Characteristics (4.8) following the evaluation of the 13th PSUR. Update of Summary of Product Characteristics	27/04/2006	08/06/2006	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/0080	Update of Summary of Product Characteristics (sections 4.2, 4.8, 5.1 and 5.2) and Package Leaflet	27/04/2006	08/06/2006	SmPC and PL	Please refer to the Scientific discussion: Karvea-H-142-II-

	to reflect pharmacokinetic, pharmacodynamic and safety information in children and adolescents. Update of Summary of Product Characteristics and Package Leaflet				80.
IB/0081	IB_10_Minor change in the manufacturing process of the active substance	29/03/2006	n/a		
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/01/2006	n/a	PL	
IB/0078	IB_10_Minor change in the manufacturing process of the active substance	16/01/2006	n/a		
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/01/2006	n/a		
II/0071	Update of Summary of Product Characteristics, Labelling and Package Leaflet following a PSUR Assessment Report and the implementation of new QRD templates. Update of Summary of Product Characteristics, Labelling and Package Leaflet	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.
IB/0077	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/11/2005	n/a		
IB/0076	IB_10_Minor change in the manufacturing process of the active substance	15/11/2005	n/a		

IA/0074	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		
IA/0073	IA_01_Change in the name and/or address of the marketing authorisation holder	20/09/2005	n/a	SmPC, Labelling and PL	
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/09/2005	n/a	PL	
IB/0068	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	16/09/2005	n/a		
IA/0070	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	15/09/2005	n/a		
IA/0069	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/0066	IB_10_Minor change in the manufacturing process of the active substance	01/09/2005	n/a		
IA/0067	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/0065	IA_11_b_Change in batch size of active substance or intermediate - downscaling	03/08/2005	n/a		
IB/0064	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	11/04/2005	n/a	Annex II and PL	

	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				
IA/0063	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	
IA/0062	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/09/2004	n/a		
IB/0061	IB_10_Minor change in the manufacturing process of the active substance	10/08/2004	n/a		
II/0055	Update of Summary of Product Characteristics, Labelling and Package Leaflet	03/06/2004	02/08/2004	SmPC, Labelling and PL	
IB/0060	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	29/07/2004	n/a		
IB/0059	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	28/07/2004	n/a		
IB/0056	IB_10_Minor change in the manufacturing process of the active substance	01/07/2004	n/a		
IA/0058	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/0057	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/0054	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	14/04/2004	n/a		
X/0050	X-3-iv_Change or addition of a new pharmaceutical form	22/10/2003	02/03/2004	SmPC, Annex II, Labelling and PL	
IB/0053	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/0051	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	31/10/2003	12/11/2003		
I/0052	IB_10_Minor change in the manufacturing process of the active substance	10/11/2003	n/a		
II/0044	Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	30/07/2003	SmPC and PL	
I/0048	12_Minor change of manufacturing process of the active substance	12/06/2003	19/06/2003		
I/0049	12_Minor change of manufacturing process of the active substance	12/06/2003	n/a		
I/0047	11_Change in or addition of manufacturer(s) of	23/04/2003	25/04/2003		

	active substance				
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/04/2003	19/05/2003	PL	
I/0046	20a_Extension of shelf-life or retest period of the active substance	21/03/2003	01/04/2003		
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2003	07/03/2003	PL	
I/0042	12_Minor change of manufacturing process of the active substance	19/12/2002	17/01/2003		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2002	16/01/2003	PL	
R/0038	Renewal of the marketing authorisation.	25/07/2002	29/10/2002	SmPC, Annex II, Labelling and PL	
I/0039	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	
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2002	28/06/2002	PL	
I/0036	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	10/04/2002	02/05/2002		

I/0037	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	10/04/2002	30/04/2002		
I/0033	01_Change following modification(s) of the manufacturing authorisation(s)	11/01/2002	12/04/2002	Annex II and PL	
II/0023	Update of Summary of Product Characteristics and Package Leaflet	20/09/2001	10/04/2002	SmPC and PL	
I/0035	01_Change following modification(s) of the manufacturing authorisation(s)	22/12/2001	08/03/2002	Annex II and PL	
I/0032	04_Replacement of an excipient with a comparable excipient	12/10/2001	27/02/2002		
I/0034	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/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/0031	03_Change in the name and/or address of the marketing authorisation holder	20/09/2001	n/a	SmPC, Labelling and PL	
I/0022	12_Minor change of manufacturing process of the active substance	26/04/2001	n/a		
II/0020	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	23/04/2001	SmPC and PL	
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	
I/0019	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	21/11/2000	n/a		
II/0017	Update of Summary of Product Characteristics and Package Leaflet	27/07/2000	16/11/2000	SmPC and PL	

N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/06/2000	27/07/2000	PL	
I/0015	12_Minor change of manufacturing process of the active substance	21/12/1999	22/05/2000		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	16/12/1999	03/05/2000	SmPC, Annex II, Labelling and PL	
I/0013	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	08/09/1999	22/09/1999		
I/0011	01_Change following modification(s) of the manufacturing authorisation(s)	28/04/1999	16/06/1999	Annex II and PL	
I/0012	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	01/06/1999	n/a		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	16/12/1998	13/04/1999	SmPC, Annex II and PL	
I/0010	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	13/01/1999	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	23/10/1998	n/a		

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