Karvezide

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/0218	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/08/2024		PL	
IA/0217	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				
WS/2502	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 5.3 of the SmPC in order to update information on hydrochlorothiazide monocomponent based on literature review. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2024	22/05/2024	SmPC	Section 5.3 of the SmPC has been updated to state that evidence of a genotoxic or carcinogenic effect was observed in some experimental models.
IG/1675	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	27/10/2023	22/05/2024	Annex II	
N/0215	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/06/2023	22/05/2024	PL	
WS/2452	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 obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/05/2023	22/05/2024	Annex II	
T/0212	Transfer of Marketing Authorisation	23/11/2022	12/12/2022	SmPC, Labelling and	

	Transfer of Marketing Authorisation			PL	
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		
WS/2267/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.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.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)	16/06/2022	n/a		
PSUSA/10601 /202108	Periodic Safety Update EU Single assessment - irbesartan, irbesartan / hydrochlorothiazide	07/04/2022	n/a		PRAC Recommendation - maintenance
IG/1451	A.7 - Administrative change - Deletion of manufacturing sites	15/02/2022	13/09/2022	Annex II and PL	
IB/0208	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/02/2022	13/09/2022	SmPC 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 obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/09/2021	13/09/2022	Annex II	Update of Annex II of the product information and lifting of condition D.
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	
A31/0188	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 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	12/11/2020	12/02/2021	Annex II	Please refer to the assessment report: Karvezide EMEA/H/A-31/1471/C/221/0188

	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 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	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 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

	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				Product Characteristics.
IB/0201	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2020	10/05/2021	SmPC and PL	
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/0196/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.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	07/05/2020	10/05/2021	Annex II	

	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/0195	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2020	10/05/2021	PL	
IG/1186	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	20/12/2019	n/a		
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/0192/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/1076	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	05/04/2019	n/a		
IG/1022	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	18/12/2018	n/a		
IAIN/0190	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2018	02/04/2019	SmPC and PL	
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	20/09/2018	SmPC, Labelling and PL	

IG/0890	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	22/02/2018	n/a		
IB/0185/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	19/09/2017	20/09/2018	Annex II and PL	
PSUSA/1653/ 201609	Periodic Safety Update EU Single assessment - hydrochlorothiazide / irbesartan	22/06/2017	24/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1653/201609.
IG/0830	A.7 - Administrative change - Deletion of manufacturing sites	22/08/2017	n/a		

IB/0183	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/0182/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/0179/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		

IA/0178/G	This was an application for a group of variations. 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 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	07/11/2016	n/a		
N/0177	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2015	24/08/2017	PL	
N/0176	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2015	24/08/2017	PL	
IB/0175	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		
A31/0165	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-	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.

	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.				
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		
PSUSA/1653/ 201309	Periodic Safety Update EU Single assessment - hydrochlorothiazide / irbesartan	13/06/2014	n/a		PRAC Recommendation - maintenance
IA/0173	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		
IA/0172	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/04/2014	n/a		
IA/0171/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	31/03/2014	n/a		

	relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer 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				
IA/0169	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	31/03/2014	n/a		
IA/0170	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	21/03/2014	n/a		
N/0168	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2014	04/09/2014	PL	
IG/0327	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/08/2013	n/a		
II/0158	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.	27/06/2013	31/07/2013	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion "Karvezide-EMEA-H-C-0221-II-158".

	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/0164	A.7 - Administrative change - Deletion of manufacturing sites	05/06/2013	31/07/2013	Annex II and PL	
IB/0161	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		
IAIN/0163	B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	02/05/2013	n/a		
IA/0162	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/0159	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/0160	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/0157	Transfer of Marketing Authorisation	01/02/2013	18/02/2013	SmPC, Labelling and PL	Transfer of the Marketing Authorisation to sanofi-aventis groupe, France.
IA/0155	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	20/12/2012	n/a		
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0154	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2012	n/a		
IB/0153/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		

II/0151	This type II variation application concerns an update of section 4.4 of the SmPC to include a warning on the risk of 'acute myopia' and 'secondary acute angle-closure glaucoma' associated with the use of hydrochlorothiazide. Further, section 4.8 of the SmPC has been updated to include the two ADRs 'acute myopia' and 'secondary acute angle-closure glaucoma' and the Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to implement editorial changes to the annexes and to revise the annexes in line with the latest QRD template (version 8.1). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	A total of six cases of 'Acute Myopia' and 'Secondary Acute Angle-Closure Glaucoma' were identified following a comprehensive literature review by the MAH. Two of them were considered related to the combination of irbesartan and HCTZ. Five cases reported bilateral 'acute angle-closure glaucoma' and one reported 'acute myopia' and 'perimacular oedema'. It is acknowledged that concomitant drugs and medical history are potential confounding factors in all cases identified, but nevertheless a role of HTCZ in these cases cannot be ruled out. Although the number of reported cases of 'acute angle-closure glaucoma' and 'acute myopia' is very small, the CHMP was of the view that this information should be reflected as a warning in the SmPC due to the seriousness of these ADRs that can lead to important visual disability, and the fact that other sulfa-derivated drugs have also been reported to cause the ADRs bilateral 'acute myopia' and 'acute angle-closure glaucoma'. Therefore, it was agreed to add the following warning to the SmPC: "'Acute Myopia and Secondary Acute Angle-Closure Glaucoma: sulfonamide drugs or sulfonamide derivative drugs can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. While hydrochlorothiazide is a sulfonamide, only isolated cases of acute angle-closure glaucoma have been reported so far with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as

					rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy." The overall benefit-risk balance for the combination irbesartan + HCTZ remains unchanged.
IB/0152	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	21/06/2012	n/a		
IB/0150/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/03/2012	n/a		
IA/0149	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/0147	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 A 45/46, or amendments to reflect a Core SPC - Change(s)	16/02/2012	27/06/2012	SmPC and PL	

	with new additional data submitted by the MAH 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				
IA/0148/G	This was an application for a group of variations. 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 B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	19/01/2012	n/a		
IB/0145	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/0144	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/0146	B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation	04/01/2012	n/a		
WS/0171	This was an application for a variation following a worksharing procedure according to Article 20 of	22/09/2011	20/10/2011	SmPC	This type IB variation concerns an update of SmPC sections 4.6 and 5.3, upon request by CHMP, with agreed wording

	Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics 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				regarding fertility. 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. This application was submitted following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
WS/0147	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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 A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.3.b - Implementation of change(s) requested	21/07/2011	18/08/2011	SmPC and PL	This type II variation concerns an update of section 4.5 of the SmPC, upon request by the CHMP following the assessment of PSUR 9, to include information about the potential interaction between hydrochlorothiazide and carbamazepine. Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatraemia. Therefore, electrolytes should be monitored during concomitant use, and if possible, another class of diuretics should be used. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to put the annexes in line with the latest QRD template (version 7.3.1). This application was submitted as a Type II variation following a worksharing procedure according to Article 20

	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				of Commission Regulation (EC) No 1234/2008.
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 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	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. 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	08/04/2011	n/a		

	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				
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/0136/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	
IA/0135	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/0134	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/0133	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/0132	To change the phone number of the Slovak local representative in the Package Leaflet. Furthermore the Marketing Authorisation Holder took this opportunity to make linguistic amendments to the Dutch and French Package Leaflets. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2010	n/a	PL	
IA/0131/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	
II/0127	Update of SPC section 4.8 upon request by CHMP following the assessment of the renewal of Karvezide (EMEA/H/C/000221/R/0114), with respect to the	17/12/2009	03/02/2010	SmPC	This Type II variation was submitted in order to update section 4.8 (Undesirable effects) of the SmPC based on a request from the CHMP following the assessment of the

	introductory paragraph and the estimate of the overall percentage of treated patients to experience adverse reactions. Update of Summary of Product Characteristics				renewal of Karvezide to provide information on adverse reactions according to the EU SmPC Guideline (October 2005), as well as to include a general description on what are the most serious and/or most frequently occurring adverse drug reactions. In support to this application, the MAH submitted a review of the Integrated Summary of Safety (ISS) as well as cumulative data from placebo-controlled hypertensive trials CV131-037,-038,-039, and -040. The updated section 4.8 includes now the following paragraph: Irbesartan/hydrochlorothiazide combination: Among 898 hypertensive patients who received various doses of irbesartan/hydrochlorothiazide (range: 37.5 mg/6.25 mg to 300 mg/25mg) in placebo-controlled trials, 29.5% of the patients experienced adverse reactions. The most commonly reported ADRs were dizziness (5.6%), fatigue (4.9%), nausea/vomiting (1.8%), and abnormal urination (1.4%). In addition, increases in blood urea nitrogen (BUN) (2.3%), creatine kinase (1.7%) and creatinine (1.1%) were also commonly observed in the trials. Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled trials.
IB/0130	IB_38_c_Change in test procedure of finished product - other changes	07/01/2010	n/a		
II/0128	Update of Summary of Product Characteristics (SPC) section 4.5 and Package Leaflet section 2 regarding information on the interaction of hydrochlorothiazide (HCTZ) with cholestyramin and colestipol resins. In	19/11/2009	21/12/2009	SmPC and PL	With this application, in SPC section 4.5 the existing statement regarding an interaction with colestyramine and colestipol resins has been amended indicating that irbesartan + hydrochlorothiazide should be taken at least

	particular to provide further guidance in the SPC to physicians on the recommended time between the administration of irbesartan + HCTZ and cholestyramin and colestipol resins. Update of Summary of Product Characteristics and Package Leaflet				one hour before or four hours after these medications. A literature search was performed by the MAH to identify studies leading to a drug interaction between irbesartan, hydrochlorothiazide and cholestyramine. In a study with ten healthy adult male subjects evaluating appropriate dosing schedules of cholestyramine to minimize its effect on absorption, the investigators reported that the best dosing schedule for cholestyramine is 4 hours after hydrochlorothiazide (Hunninghake and Hibbard, 1986). On the other hand, it has been recommended that the administration of cholestyramine or colestipol have to be separated from the time of other medications (e.g. HCTZ) by 1-2 hours to minimize their effects on the absortion (Lamrini et al 1997; Hunninghake et al 1982).
IB/0129	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	02/12/2009	n/a		
N/0126	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2009	n/a	PL	
II/0125	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	05/10/2009		
IA/0124	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/07/2009	n/a		
IA/0123	IA_11_a_Change in batch size of active substance or	26/06/2009	n/a		

	intermediate - up to 10-fold				
IB/0120	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	23/06/2009	n/a	PL	
IA/0122	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	10/06/2009	n/a	PL	
IA/0121	IA_32_a_Change in batch size of the finished product - up to 10-fold	20/05/2009	n/a		
IB/0119	IB_10_Minor change in the manufacturing process of the active substance	17/04/2009	n/a		
II/0118	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	27/03/2009	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/0117	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.
R/0114	Renewal of the marketing authorisation.	24/07/2008	01/10/2008	SmPC, Labelling and PL	Based on the CHMP review of the available information and on the basis of the re-evaluation of the benefit-risk balance, 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 Karvezide continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
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	18/08/2008	n/a		
IA/0115	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	24/04/2008	10/06/2008	SmPC 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

	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 and Package Leaflet				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	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	08/05/2008	n/a	Annex II and PL	
IB/0113	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	07/05/2008	n/a	SmPC	
IB/0112	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		
IA/0107	IA_09_Deletion of manufacturing site	13/12/2007	n/a		
N/0106	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/12/2007	n/a	PL	
IA/0105	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	27/09/2007	n/a		
IB/0104	IB_10_Minor change in the manufacturing process of the active substance	21/09/2007	n/a		
N/0103	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/08/2007	n/a	PL	
IB/0102	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	22/08/2007	n/a	Annex II and PL	
N/0098	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2007	n/a	PL	

IB/0100	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	07/06/2007	n/a	PL	
IB/0099	IB_33_Minor change in the manufacture of the finished product	21/05/2007	n/a		
IA/0101	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	15/05/2007	n/a		
IA/0097	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	23/03/2007	n/a		
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/0094	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/0093	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_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/0091	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/0090	IA_05_Change in the name and/or address of a manufacturer of the finished product	15/01/2007	n/a	Annex II and PL	
II/0074	This variation refers to changes in section 5.1 of the SPC to include the results of a trial studying the use of CoAprovel as 1st line treatment in patients with severe hypertension. The product information has also been updated according to the latest QRD templates. Update of Summary of Product Characteristics, Labelling and Package Leaflet	16/11/2006	11/01/2007	SmPC, Annex II, Labelling and PL	Efficacy and safety of Karvezide as initial therapy for severe hypertension (defined as SeDBP 110 mmHg) was evaluated in a multicentre, randomised, double-blind, active-controlled, 8-week, parallel-arm study. A total of 697 patients were randomised in a 2:1 ratio to either irbesartan/hydrochlorothiazide 150 mg/12.5 mg or to irbesartan 150 mg and systematically force-titrated (before assessing the response to the lower dose) after one week to irbesartan/hydrochlorothiazide 300 mg/25 mg or irbesartan 300 mg, respectively. The study recruited 58% males. The mean age of patients was 52.5 years, 13% were 65 years of age, and just 2% were 75 years of age. Twelve percent (12%) of patients were diabetic, 34% were hyperlipidemic and the most frequent cardiovascular condition was stable angina pectoris in 3.5% of the participants. The primary objective of this study was to compare the proportion of patients whose SeDBP was controlled (SeDBP < 90 mmHg) at Week 5 of treatment. Forty-seven percent (47.2%) of patients on the combination achieved trough SeDBP < 90 mmHg compared to 33.2% of patients on irbesartan (p = 0.0005). The mean baseline BP was

					approximately 172/113 mmHg in each treatment group and decreases of SeSBP/SeDBP at 5 weeks were 30.8/24.0 mmHg and 21.1/19.3 mmHg for irbesartan/hydrochlorothiazide and irbesartan, respectively ($p < 0.0001$). The types and incidences of adverse events reported for patients treated with the combination were similar to the adverse event profile for patients on monotherapy. During the 8 week treatment period, there were no reported cases of syncope in either treatment group. There were 0.6% and 0% of patients with hypotension and 2.8% and 3.1% of patients with dizziness as adverse reactions reported in the combination and monotherapy groups, respectively.
IA/0089	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	09/01/2007	n/a		
IA/0088	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	12/12/2006	n/a		
IA/0087	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/0085	IB_10_Minor change in the manufacturing process of the active substance	29/11/2006	n/a		
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2006	n/a	PL	
IB/0084	IB_33_Minor change in the manufacture of the finished product	10/11/2006	n/a		

	IA_32_a_Change in batch size of the finished product - up to 10-fold				
IA/0083	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	11/09/2006	n/a		
IA/0082	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		
X/0071	Annex I_2.(c) Change or addition of a new strength/potency	28/06/2006	28/08/2006	SmPC, Labelling and PL	The new presentation consist in one new tablet strength 300/25 mg of film-coated tablets (irbesartan and hydrochlorothiazide). Pack sizes are: 14, 28, 56, 84 and 98 blister packs and 56 unit-dose blister pack. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. The bioequivalence study performed by the MAH is considered the most sensitive design to detect differences in the performance of the formulations. The trial was able to adequately characterise the exposure to irbesartan and hydrochlorothiazide, and demonstrated that all three formulations, 300 mg/25 mg coated and uncoated Irbesartan/ hydrochlorothiazide Tablets and 2 150 mg/12.5 mg Avalide Tablets, are bioequivalent.
IB/0081	IB_10_Minor change in the manufacturing process of the active substance	21/08/2006	n/a		
IA/0080	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/07/2006	n/a		

IA/0079	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/07/2006	n/a		
IA/0078	IA_09_Deletion of manufacturing site	11/07/2006	n/a	Annex II and PL	
IB/0075	IB_10_Minor change in the manufacturing process of the active substance	28/06/2006	n/a		
IA/0077	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	22/06/2006	n/a		
IA/0076	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	20/06/2006	n/a		
IB/0073	IB_10_Minor change in the manufacturing process of the active substance	29/03/2006	n/a		
II/0069	Quality changes	26/01/2006	06/02/2006		
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/01/2006	n/a	PL	
IB/0070	IB_10_Minor change in the manufacturing process of the active substance	16/01/2006	n/a		
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/01/2006	n/a		
IB/0068	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/11/2005	n/a		

IB/0067	IB_10_Minor change in the manufacturing process of the active substance	15/11/2005	n/a		
IA/0065	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/0064	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/0063	IA_01_Change in the name and/or address of the marketing authorisation holder	20/09/2005	n/a	SmPC, Labelling and PL	
IB/0060	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	16/09/2005	n/a		
IA/0062	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	15/09/2005	n/a		
IA/0061	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/0058	IB_10_Minor change in the manufacturing process of the active substance	01/09/2005	n/a		
IA/0059	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/0057	IA_11_b_Change in batch size of active substance or intermediate - downscaling	03/08/2005	n/a		

IA/0056	IA_05_Change in the name and/or address of a manufacturer of the finished product	10/02/2005	n/a	SmPC, Annex II, Labelling and PL	
IB/0055	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	13/01/2005	n/a	Annex II and PL	
II/0044	Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	28/10/2004	SmPC and PL	
IA/0054	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/09/2004	n/a		
IB/0053	IB_10_Minor change in the manufacturing process of the active substance	10/08/2004	n/a		
II/0046	Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	02/08/2004	SmPC and PL	
IB/0052	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	29/07/2004	n/a		
IB/0051	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	28/07/2004	n/a		
IB/0048	IB_10_Minor change in the manufacturing process of the active substance	01/07/2004	n/a		
IA/0050	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	30/06/2004	n/a	Annex II and PL	

	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing				
IA/0049	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/0047	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	20/04/2004	n/a		
IB/0045	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	14/04/2004	n/a		
X/0040	X-3-iv_Change or addition of a new pharmaceutical form	22/10/2003	02/03/2004	SmPC, Annex II, Labelling and PL	
R/0041	Renewal of the marketing authorisation.	25/09/2003	04/12/2003	SmPC, Annex II, Labelling and PL	
I/0042	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	31/10/2003	12/11/2003		
I/0043	IB_10_Minor change in the manufacturing process of the active substance	10/11/2003	n/a		
II/0037	Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	02/10/2003	SmPC and PL	

I/0039	12_Minor change of manufacturing process of the active substance	12/06/2003	26/06/2003		
I/0038	12_Minor change of manufacturing process of the active substance	11/06/2003	26/06/2003		
I/0036	11_Change in or addition of manufacturer(s) of active substance	23/04/2003	25/04/2003		
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/04/2003	16/05/2003	PL	
I/0035	20a_Extension of shelf-life or retest period of the active substance	21/03/2003	01/04/2003		
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2003	07/03/2003	PL	
I/0032	12_Minor change of manufacturing process of the active substance	19/12/2002	17/01/2003		
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2002	15/01/2003	PL	
I/0029	15_Minor changes in manufacture of the medicinal product	05/06/2002	18/06/2002		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2002	28/06/2002	PL	
I/0026	24a_Change in test procedure for starting material/intermediate used in manuf. of active	10/04/2002	02/05/2002		

	substance				
I/0028	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	10/04/2002	30/04/2002		
I/0027	20_Extension of shelf-life as foreseen at time of authorisation	20/02/2002	18/04/2002	SmPC	
II/0018	Update of Summary of Product Characteristics and Package Leaflet	20/09/2001	10/04/2002	SmPC and PL	
I/0025	01_Change following modification(s) of the manufacturing authorisation(s)	22/12/2001	08/03/2002	Annex II and PL	
I/0024	04_Replacement of an excipient with a comparable excipient	12/10/2001	26/02/2002		
I/0022	30_Change in pack size for a medicinal product	20/09/2001	19/02/2002	SmPC, Labelling and PL	
I/0021	30_Change in pack size for a medicinal product	20/09/2001	19/02/2002	SmPC, Labelling and PL	
I/0020	30_Change in pack size for a medicinal product	13/07/2001	08/10/2001	SmPC, Labelling and PL	
I/0019	30_Change in pack size for a medicinal product	13/07/2001	08/10/2001	SmPC, Labelling and PL	

I/0023	03_Change in the name and/or address of the marketing authorisation holder	20/09/2001	n/a	SmPC, Labelling and PL	
I/0017	12_Minor change of manufacturing process of the active substance	26/04/2001	n/a		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	23/04/2001	SmPC and PL	
I/0016	01_Change following modification(s) of the manufacturing authorisation(s)	04/04/2001	n/a	Annex II and PL	
I/0015	26_Changes to comply with supplements to pharmacopoeias	20/03/2001	n/a		
I/0013	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	21/11/2000	n/a		
II/0012	Update of Summary of Product Characteristics and Package Leaflet	27/07/2000	16/11/2000	SmPC and PL	
I/0009	12_Minor change of manufacturing process of the active substance	21/12/1999	20/05/2000		
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/01/2000	24/03/2000	PL	
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/11/1999	03/02/2000	PL	

I/0008	15_Minor changes in manufacture of the medicinal product	08/09/1999	22/09/1999		
I/0007	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	08/09/1999	22/09/1999		
I/0006	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	01/06/1999	07/06/1999		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/03/1999	07/05/1999	PL	
I/0004	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	19/02/1999	n/a		
I/0003	16_Change in the batch size of finished product	19/02/1999	n/a		
I/0002	11_Change in or addition of manufacturer(s) of active substance	05/02/1999	n/a		
I/0001	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/01/1999	n/a		