Irbesartan Hydrochlorothiazide Zentiva

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0127	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/04/2023		SmPC and PL	
IB/0126/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or	09/03/2023	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).

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	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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)				
IAIN/0125	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	27/09/2022		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).
N/0124	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/08/2022		Labelling	
IB/0122/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	21/07/2022	n/a		

	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				
IB/0123/G	This was an application for a group of variations. B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) 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.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur. 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.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	14/07/2022		Annex II and PL	

	or addition) for the AS or a starting material/intermediate B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling				

	down to 10-fold B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation 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)				
PSUSA/10601 /202108	Periodic Safety Update EU Single assessment - irbesartan, irbesartan / hydrochlorothiazide	07/04/2022	n/a		PRAC Recommendation - maintenance
IB/0120	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/04/2022	07/06/2022	SmPC and PL	To update sections 4.4 and 4.8 of the SmPC regarding the risk of acute respiratory distress syndrome (ARDS) linked to hydrochlorothiazide. The Package Leaflet has been updated in accordance.
IB/0121/G	This was an application for a group of variations. 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.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	23/02/2022	n/a		
IB/0118	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished	04/01/2022	n/a		

	product - Other variation				
IB/0117	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/08/2021	07/06/2022	Annex II	
IB/0115	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	14/07/2021	n/a		
IB/0116	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	11/06/2021	07/06/2022	SmPC, Labelling and PL	
IAIN/0114	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	18/05/2021	07/06/2022	Annex II	
IB/0113/G	This was an application for a group of variations. 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	11/05/2021	n/a		

	deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
IB/0111/G	This was an application for a group of variations. B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	12/04/2021	04/06/2021	Annex II and PL	

	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.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.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material 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.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.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				
IAIN/0112	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)	19/03/2021	n/a		
A31/0101	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 15 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	12/11/2020	19/02/2021	Annex II	Please refer to the assessment report: Irbesartan Hydrochlorothiazide Zentiva EMEA/H/A-31/1471/C/783/0101

	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.				
IA/0110	A.7 - Administrative change - Deletion of manufacturing sites	13/10/2020	04/06/2021	Annex II and PL	
IA/0109/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.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.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	07/09/2020	n/a		

IB/0108	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2020	04/06/2021	SmPC and PL	
IB/0107/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 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	27/05/2020	04/06/2021	Annex II	

	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				
IA/0106	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	06/03/2020	n/a		
IB/0105/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	14/10/2019	n/a		
IG/1076	B.III.1.a.2 - Submission of a new/updated or	05/04/2019	n/a		

	deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
IAIN/0103	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2018	15/04/2019	SmPC and PL	
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		
T/0100	Transfer of Marketing Authorisation	18/09/2018	08/11/2018	SmPC, Labelling 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	08/11/2018	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/0096/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	08/11/2018	Annex II and PL	
PSUSA/1653/ 201609	Periodic Safety Update EU Single assessment - hydrochlorothiazide / irbesartan	22/06/2017	28/08/2017	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/0095	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/0094/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/0091/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	05/01/2017	n/a		

	variation				
IA/0090/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/0089	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/09/2015		PL	
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2015		PL	
IB/0087	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		
A31/0075	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	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.

	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.				
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/0085	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/0084	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/0083/G	This was an application for a group of variations.	31/03/2014	n/a		

	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				
IA/0081	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/0082	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/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/03/2014	04/09/2014	PL	
IAIN/0078	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/10/2013	n/a		
IG/0327	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/08/2013	n/a		
II/0069	Update of SmPC sections 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor	27/06/2013	31/07/2013	SmPC, Annex II, Labelling	Please refer to the Scientific Discussion "Irbesartan Hydrochlorothiazide Zentiva-EMEA-H-C-0783-II69".

	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			and PL	
IA/0076	A.7 - Administrative change - Deletion of manufacturing sites	05/06/2013	31/07/2013	Annex II and PL	
IB/0072	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/0074	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/0073	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	26/04/2013	n/a		

	of an obsolete parameter				
II/0070	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/0071	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	22/04/2013	n/a		
IAIN/0068	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/01/2013	n/a		
IA/0067	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		
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2012	n/a		
T/0063	Transfer of Marketing Authorisation	10/09/2012	12/11/2012	SmPC, Labelling and PL	Transfer of the Marketing Authorisation to sanofi-aventis groupe, France.
IAIN/0065	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/10/2012	n/a		

IB/0064/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/0060	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/0062	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		
IAIN/0061	A.1 - Administrative change - Change in the name and/or address of the MAH	03/04/2012	27/06/2012	SmPC, Labelling and PL	
IB/0059/G	This was an application for a group of variations.	13/03/2012	n/a		

	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)				
R/0049	Renewal of the marketing authorisation.	20/10/2011	27/02/2012		Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP was 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 Irbesartan Hydrochlorothiazide Winthrop continues to be favourable. The CHMP recommended the renewal of the Marketing Authorisation for Irbesartan Hydrochlorothiazide Winthrop, subject to the conditions as laid down in Annex II to the Opinion. The CHMP was also of the opinion that the renewal can be granted with unlimited validity. The renewal required no amendments to the terms of the Community Marketing Authorisation
IA/0058	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/0055	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	16/02/2012	27/06/2012	SmPC and PL	

IAIN/0057/G	This was an application for a group of variations. A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	06/02/2012	27/06/2012	SmPC, Annex II, Labelling and PL	
IA/0056/G	This was an application for a group of variations.	19/01/2012	n/a		

	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				
IB/0053	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/0052	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/0054	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 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	22/09/2011	24/10/2011	SmPC	This type IB variation concerns an update of SmPC sections 4.6 and 5.3, upon request by CHMP, with agreed wording 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 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	21/07/2011	07/09/2011	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 of Commission Regulation (EC) No 1234/2008.
WS/0074	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	14/04/2011	16/06/2011	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

	Update of Summary of Product Characteristics and Package Leaflet C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				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/0048	A.7 - Administrative change - Deletion of manufacturing sites	27/05/2011	n/a		
IA/0047	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/0044/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	11/04/2011	n/a		
IA/0045	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons	08/04/2011	n/a	Annex II	

	or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD				
IB/0046	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		
T/0043	Transfer of Marketing Authorisation	24/11/2010	06/01/2011	SmPC, Labelling and PL	
IA/0042/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/0041	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/0040	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/0039	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/0038	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/0037/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/0033	Update of SPC section 4.8 upon request by CHMP following the assessment of the renewal of the reference medicinal product CoAprovel (EMEA/H/C/000222/R/0108), with respect to the introductory paragraph and the estimate of the overall percentage of treated patients to experience	17/12/2009	04/02/2010	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 renewal of the reference medicinal product CoAprovel to provide information on adverse reactions according to the EU SmPC Guideline (October 2005), as well as to include a

	adverse reactions. Update of Summary of Product Characteristics				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/0036	IB_38_c_Change in test procedure of finished product - other changes	07/01/2010	n/a		
II/0034	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 particular to provide further guidance in the SPC to physicians on the recommended time between the administration of irbesartan + HCTZ and	19/11/2009	21/12/2009	SmPC and PL	With this application, 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 one hour before or four hours after these medications. A literature search was performed by the MAH to identify

	cholestyramin and colestipol resins. Update of Summary of Product Characteristics and Package Leaflet				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/0035	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	02/12/2009	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/10/2009	n/a	PL	
II/0031	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	08/10/2009		
IA/0030	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/07/2009	n/a		
IB/0026	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IB_07_c_Replacement/add. of manufacturing site:	23/06/2009	n/a	PL	

	All other manufacturing operations ex. batch release IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms				
IA/0029	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	22/06/2009	n/a		
IA/0028	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/0027	IA_32_a_Change in batch size of the finished product - up to 10-fold	20/05/2009	n/a		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2009	n/a	PL	
II/0023	Update of SPC sections 2, 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 6.1 as well as the package leaflet to align the Product Information of Irbesartan Hydrochlorotihazide Winthrop with the Product Information of the reference product CoAprovel. Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	17/04/2009	SmPC and PL	The SPC and Package Leaflet of Irbesartan Hydrochlorothiazide Winthrop have been aligned with the Product Information of the reference product CoAprovel as approved with the renewal procedure.
IB/0024	IB_10_Minor change in the manufacturing process of the active substance	17/04/2009	n/a		
II/0022	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	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.

	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				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/0021	Update of Detailed Description of the Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	06/03/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 3.0) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
IB/0020	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/0019	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/07/2008	n/a		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	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

	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 and Package Leaflet				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/0016	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	PL	
IB/0018	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	07/05/2008	n/a	SmPC	
IB/0017	IB_10_Minor change in the manufacturing process of the active substance	25/04/2008	n/a		

	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold				
IA/0015	IA_09_Deletion of manufacturing site	03/04/2008	n/a		
IA/0013	IA_09_Deletion of manufacturing site	13/02/2008	n/a		
IA/0012	IA_09_Deletion of manufacturing site	14/12/2007	n/a		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/12/2007	n/a	PL	
IB/0009	IB_10_Minor change in the manufacturing process of the active substance	21/09/2007	n/a		
IA/0010	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	20/09/2007	n/a		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/08/2007	n/a	PL	
IB/0007	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	
IB/0005	IB_07_c_Replacement/add. of manufacturing site:	07/06/2007	n/a	PL	

	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				
IB/0004	IB_33_Minor change in the manufacture of the finished product	21/05/2007	n/a		
IA/0006	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	15/05/2007	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2007	n/a	PL	
IA/0003	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	23/03/2007	n/a		