Copalia

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
IG/1804	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	21/11/2024		Annex II and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

IG/1784	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	28/08/2024	n/a		
IG/1763	A.7 - Administrative change - Deletion of manufacturing sites	04/07/2024	n/a		
IG/1708	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	08/04/2024	n/a		
WS/2610	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/01/2024		SmPC and PL	
IG/1666/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.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	14/09/2023	n/a		

IG/1644/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	08/08/2023	n/a		
IG/1637	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	19/07/2023	n/a		
WS/2363/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.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	02/03/2023	n/a		

	in the manufacturing process 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 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				
IG/1598/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	28/02/2023	n/a		
WS/2337/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. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation 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	10/11/2022	06/11/2023	SmPC and Annex II	C.I.z - To update section 4.9 of the SmPC, to implement the wording related to the risk of non-cardiogenic pulmonary oedema in amlodipine overdose. C.I.11.a - To update Annex II to reflect the fulfilment of Condition B, as set out by the Commission Decision as an outcome of the assessment for the impact of the Article 5(3) scientific opinion on nitrosamines in human medicinal products on the opinion adopted pursuant to Article 31 of Directive 2001/83/EC for angiotensin-II-receptor antagonists (sartans) containing a tetrazole group.

WS/2278/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) 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	27/10/2022	n/a		
WS/2256/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.III.1.a.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.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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/06/2022	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.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				
PSUSA/10344 /202106	Periodic Safety Update EU Single assessment - amlodipine / valsartan, amlodipine / hydrochlorothiazide / valsartan	10/02/2022	n/a		PRAC Recommendation - maintenance
IG/1439/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 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	15/10/2021	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IG/1438/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	05/10/2021	29/09/2022	Annex II and PL	
WS/2109	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	02/09/2021	11/10/2021	Annex II	
IG/1383/G	This was an application for a group of variations. 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 C.I.11.a - Introduction of, or change(s) to, the	26/04/2021	11/10/2021	Annex II	

	obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority				
WS/2041/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.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.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/04/2021	n/a		
WS/2019	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue	15/04/2021	n/a		

WS/2022/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.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.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.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	15/04/2021	n/a		
WS/2023/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.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.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-	25/03/2021	11/10/2021	Annex II and PL	

	release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products				
A31/0099	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 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	12/11/2020	12/02/2021	Annex II	Please refer to the assessment report: Copalia EMEA/H/A-31/1471/C/774/0099

	the Marketing Authorisations should be varied.				
WS/1946	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	14/01/2021	n/a		
IG/1319	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	07/12/2020	n/a		
IB/0112/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.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.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a	20/10/2020	11/10/2021	Annex II	

	specification parameter as a result of a safety or quality issue 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.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation 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 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 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)				

IG/1254/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.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	15/05/2020	n/a		
IG/1174/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	11/12/2019	n/a		
WS/1656/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.a.1.f - Change in the manufacturer of AS or of a	31/10/2019	26/06/2020	Annex II	

	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.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.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
IG/1111/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 -	08/08/2019	n/a		

	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.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)				
IG/1116/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	16/07/2019	26/06/2020	Annex II and PL	
IG/1112	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	05/07/2019	n/a		
IG/1100	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		
IG/1099	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		

IG/1098	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	29/04/2019	n/a		
IG/0986	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/10/2018	02/04/2019	Annex II, Labelling and PL	
IG/0975/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.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	10/09/2018	n/a		
IG/0958/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	21/08/2018	n/a		

	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
IG/0947	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	21/06/2018	n/a		
T/0097	Transfer of Marketing Authorisation	16/05/2018	04/06/2018	SmPC, Labelling and PL	
IG/0910	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	17/04/2018	04/06/2018	SmPC and PL	
WS/1291/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.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.c - Change in the specification parameters and/or limits of an AS, starting	15/03/2018	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test				

	procedure is already authorised B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0863	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	01/12/2017	n/a		
IG/0805	A.7 - Administrative change - Deletion of manufacturing sites	23/05/2017	n/a		
PSUSA/10344 /201606	Periodic Safety Update EU Single assessment - amlodipine / valsartan, amlodipine / hydrochlorothiazide / valsartan	09/03/2017	n/a		PRAC Recommendation - maintenance
IG/0776	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	23/02/2017	n/a		
WS/1080	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/02/2017	30/01/2018	SmPC and PL	

IG/0751/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	15/12/2016	n/a		
IG/0727/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.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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/09/2016	n/a		
IG/0707	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	21/07/2016	n/a		

	batch control/testing takes place				
IG/0706	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	21/07/2016	n/a		
WS/0709	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes related to the amlodipine component Update of section 4.2 of the SmPC to include revised dosing recommendations in patients with hepatic impairment and in elderly patients. Changes related to the valsartan component Update of sections 4.2 and 4.3 of the SmPC to remove the contraindication related to patients with severe renal impairment and patients undergoing dialysis and section 4.8 of the SmPC to update the Preferred Term as per MedDRA version 17. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and the Package Leaflet C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	05/05/2015	SmPC and PL	The removal of the contraindication related to patients with severe renal impairment and patients undergoing dialysis, is editorial in nature and is implemented to align the product information with the decision from Article 30 Referral procedure (EMEA procedure number: EMEA/H/A-30/998) concluded for Diovan in Nov 2008. As an oversight, this was not applied to the Exforge product information at the time. The posology section is updated to highlight that when switching eligible hypertensive patients with hepatic impairment or elderly hypertensive patients to amlodipine or Exforge, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.
IG/0539	C.I.1.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a Union	27/03/2015		SmPC and PL	

	referral procedure - The product is not covered by the defined scope of the procedure				
IG/0536/G	This was an application for a group of variations. 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	11/03/2015	n/a		
IG/0528/G	This was an application for a group of variations.	17/02/2015	n/a		

	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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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				
IG/0523/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	22/01/2015	n/a		
IG/0514	A.1 - Administrative change - Change in the name and/or address of the MAH	16/12/2014	05/05/2015	SmPC, Labelling and PL	
WS/0632/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.	23/10/2014	n/a		To implement changes in the manufacturing process of the active substance

	To implement changes in the manufacturing process of the active substance. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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				

WS/0630/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. Replacement of 2 test methods for an active substance intermediate. To incude a minor change in a test method for an active substance intermediate. To add 3 test methods for an active substance intermediate. To change the specification parameter for an active substance 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	23/10/2014	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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.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				
WS/0629/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. To replace 3 test methods for an active substance intermediate. To include a minor change to an approved test procedure for an active susbtance intermediate. To add a test method or an active substance intermediate. To add 2 alternative test methods for an active substance intermediate. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	23/10/2014	n/a		To replace 3 test methods for an active substance intermediate. To include a minor change to an approved test procedure for an active susbatcne intermediate. To add a test method or an active substance intermediate. To add 2 alternative test methods for an active substance intermediate.

	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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.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.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				

WS/0631/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. To add an alternative manufacturer of AS intermediates. To increase the batch sizes for AS intermediates for the new manufacturing site To delete a manufacturing site for AS intermediates. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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 A.7 - Administrative change - Deletion of manufacturing sites	23/10/2014	n/a		
A31/0069	On 17 April 2013, further to the emergence of new evidence from the scientific literature on dual RAS blockade therapy and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) initiated a review under Article 31 of Council Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the combined use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor	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.

	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/0424/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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	26/03/2014	n/a		
WS/0516	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 include the ADR 'bullous dermatitis'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	04/09/2014	SmPC	The MAH has submitted a comprehensive report with the purpose of reviewing the potential association of skin events with valsartan containing medications, including Exforge and Exforge HCT and respective clones. It is considered justified to update the list of ADRs in section 4.8 'undesirable effects' of the Exforge SmPC and Exforge HCT SmPC and their respective clones based on additional information from a small number of post-marketing cases reporting bullous rash occurring with valsartan. This amendment does not change the benefit risk balance for these products which remains positive.
WS/0495/G	This was an application for a group of variations	20/02/2014	n/a		

	following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. - change in the specification limits of some intermediates used in the manufacture of the active substance, - addition of a new specification parameters with their corresponding test methods to the specification of some intermediates used in the manufacture of the active substance and - change in test procedures for some intermediates used in the manufacture of the active substance. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.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.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 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.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				

IG/0377/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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	22/11/2013	n/a		
WS/0461	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 4.5 of the SmPC to include further information regarding an interaction between valsartan and lithium. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	04/09/2014	SmPC	The MAH has reviewed the clinical databases of four large outcomes studies (Val-HeFT, Value, Valiant, and Navigator) for adverse event reports of lithium toxicity. Further, the Novartis Safety Database (ARGUS) was searched for all cases where both valsartan and lithium were reported as co-administered, and a literature search was performed for published studies. The available data suggest a possible reversible interaction between valsartan and lithium, although the exact mechanism has not been established. The data identified are limited and no confirmatory evidence was available from the clinical trials performed. The SmPC has been updated to inform prescribers of the fact that reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including valsartan. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be

					increased further.
IG/0349	B.III.1.a.4 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Deletion of certificates (in case multiple certificates exist per material)	27/08/2013	n/a		
WS/0360	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC sections 4.2, 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor Blockers (ARBs) or Angiotensin-Converting-Enzyme inhibitors (ACEi) with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus. Further, section 4.4 of the SmPC has been updated to inform prescribers that caution is required, and monitoring of blood pressure, renal function and electrolytes is recommended, when co-administering agents acting on the renin angiotensin aldosterone system (RAAS) i.e. ACEi, ARBs or aliskiren as a direct renin inhibitor. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the SmPC, Annex II and the Package Leaflet in line with the latest QRD template, to implement minor editorial changes in the Package Leaflet and to add the contact details of the Croatian local representative in the Package Leaflet. C.I.4 - Variations related to significant modifications	27/06/2013	31/07/2013	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Exforge-Copalia-Dafiro-Imprida-EMEA-H-C-xxxx-WS-360-AR".

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0270	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	01/02/2013	n/a		
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IG/0233	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	13/11/2012	n/a		
WS/0249/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. WS-0249-G was a group of variations consisting of two Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 as follows: Variation 1: Update of section 4.4 of the SmPC to add a new warning regarding the risk of 'angioedema' related to the valsartan compound. Further, the MAH took the opportunity to update the wording of the existing warnings in section 4.4 of the SmPC ('renal artery stenosis', 'heart failure', and 'aortic and mitral valve stenosis') for increased	20/09/2012	25/10/2012	SmPC and PL	The safety update of the SmPC and Package Leaflet was based on a review of the MAH's safety and clinical trial data bases, published literature for both the amlodipine and valsartan components, a recommendation by the US FDA as well as the recent revised and harmonised amlodipine monotherapy product information that was agreed by the CHMP as part of the article 30 referral procedure EMEA/H/A-30/1288 on 21 July 2011. The MAH presented an extensive analysis of both 'angioedema requiring intubation' and 'previous angioedema with or without ACE-inhibitor use', based on data from their safety database and the clinical trial database. In addition, the MAH provided the outcome of a literature search. From the safety database, 42 patients out of 1469 'angioedema' reports (2.86%) required intubation. In the clinical trial database there was a small number of

	clarity. The Package Leaflet has been updated accordingly; Variation 2: Update of sections 4.2, 4.3, 4.4, 4.7, 4.8, 5.1 and 5.2 of the SmPC to harmonise the existing wording related to the amlodipine compound in line with the latest SmPC of Norvasc (amlodipine monotherapy) approved as part of a recent article 30 procedure EMEA/H/A-30/1288. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details for the local representatives for Luxemburg and Malta in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				patients with angioedema who also experienced an AE related to 'respiratory distress' (e.g. laryngospasm, enotracheal intubation, laryngeal edema, mechanical ventilation, tracheostomy, respiratory distress, wheezing). The percentage of patients with a past history of angioedema across all studies was small. A total of 86 patients out of the 1469 reports from the safety database had a previous episode of angioedema, in 40 of these the previous angioedema episode was associated with the use of an ACE-inhibitor and in 46 patients it was not. In 5/40 and 12/46 cases, respectively, the index event was worse than the previous one. This does not indicate that a more severe angioedema event than that occurring in association with an ACE-inhibitor must necessarily be expected when valsartan is given for treatment subsequently. According to the literature, the frequency of angioedema associated with ARBs seems lower than that observed with ACE-inhibitors. Although some publications suggest a higher risk of angioedema with ARBs in patients who had already experienced angioedema with ACE-inhibitors, the frequency data reported in the literature are inconsistent. However, as angioedema is a potentially life-threatening and fatal adverse effect, the reviewed literature highlights that ACE-inhibitors or ARBs should be used with caution in patients with any history of this condition. The safety data provided by the MAH is regarded as sufficient in order to justify the proposed warning on 'angioedema' in section 4.4 of the SmPC. It should also be noted that a warning regarding 'angioedema' is already included in the SmPC for Diovan (valsartan monotherapy). Additional changes to the wording of warnings already included in SmPC section 4.4 ("renal artery stenosis",

					"heart failure" and "aortic and mitral valve stenosis") were also made as part of this procedure in order to provide further clarity to the health care professional. In addition, the MAH took the opportunity to update the amlodipine sections of the SmPC in accordance with the harmonised product information for Norvasc (amlodipine monotherapy).
WS/0248/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. WS-0248-G was a group of variations consisting of two Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 as follows: Variation 1: Update of section 4.5 of the SmPC to add information about the potential drug interaction between amlodipine and simvastatin, and update of the existing amlodipine information in section 4.5 in line with the revised drug interactions section for Norvasc (amlodipine monotherapy). The Package Leaflet has been updated accordingly; Variation 2: Update of section 4.5 of the SmPC to add information about the potential drug interaction between valsartan and inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir). The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications	19/07/2012	23/08/2012	SmPC and PL	Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects. Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required. There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine. In animals, lethal ventricular fibrillation and cardiovascular

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia. In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin. The results of an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
IG/0209/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	17/08/2012	n/a		
WS/0282	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/07/2012	19/07/2012		

	to add a new specification parameter for impurities in the active substance. 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				
IG/0199/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.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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	09/07/2012	n/a		
WS/0251/G	This was an application for a group of variations following a worksharing procedure according to	24/05/2012	28/06/2012	SmPC	The safety of amlodipine in human pregnancy has not been established. Reproductive studies in rats and mice have

	Article 20 of Commission Regulation (EC) No 1234/2008. WS-0251-G is a group of two variations (one type II & one type IB) following a worksharing procedure as follows: - Type II variation: Update of section 4.6 of the SmPC with wording on fertility in line with the SmPC for Diovan (valsartan monotherapy) and 5.3 of the SmPC to implement the changes to the SmPC for Diovan that was approved as part of a recent Article 30 (referral) procedure; - Type IB variation: Update of sections 4.6 and 5.3 of the SmPC to implement the changes to the SmPC for Norvasc (amlodipine monotherapy) that was approved as part of a recent Article 30 (referral) procedure. C.I.1.b - Change in the SPC, Labelling or PL following a referral procedure - The product is not covered by the defined scope of the referral but the change implements the outcome of the referral and no new additional data are submitted by the MAH C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells. Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. * Based on patient weight of 50 kg Valsartan had no adverse effects on the reproductive

					performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which

					produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/05/2012	28/06/2012	PL	
IG/0148/G	This was an application for a group of variations. 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 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	22/02/2012	n/a		
R/0049	Renewal of the marketing authorisation.	22/09/2011	21/11/2011	SmPC, Annex II, Labelling and PL	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 Copalia continues to be favourable. The CHMP recommended the renewal of the Marketing Authorisation for Copalia, 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 amendments to the terms of the Community Marketing Authorisation based on the CHMP's request to implement the latest QRD template. Therefore, the CHMP recommended the following annexes to be amended: I, II, IIIA and IIIB.
WS/0100/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. Update of Summary of Product Characteristics and Package Leaflet This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	23/06/2011	27/07/2011	SmPC and PL	WS-0100-G was submitted for a group of variations consisting of three Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The following variation was not considered acceptable by the CHMP: - Variation 1 (scope as applied for by the MAH): Update of section 5.1 of the SmPC with information on efficacy in patients with stage 2 hypertension and black patients based on studies VAA 2402 and VAA 2403. The following variations were considered acceptable by the CHMP: - Variation 2: Deletion of the current paragraph in section 5.1 of the SmPC that provides information on the relative efficacy of valsartan/amlodipine 80/5 mg compared to amlodipine 10 mg in relation to the incidence of oedema. In addition, the MAH took the opportunity to update the SmPC in line with the latest QRD template and to update the contact details of the local representatives in the Package Leaflet. - Variation 3: Update of section 5.1 of the SmPC with information on efficacy in obese patients. [cross reference to Scientific discussion of adopted CHMP Assessment Report].

	clinical, clinical or pharmacovigilance data				
IG/0088/G	This was an application for a group of variations. 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 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	11/07/2011	n/a		
IG/0074/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.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.c - Change in the specification parameters and/or limits of an AS, starting	17/06/2011	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IG/0058	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	13/04/2011	n/a		
WS/0088/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. to change the specification limit for an impurity in the active substance ; to add new test procedures for the active substance to add new specifications in the active substance to delete a test procedure for the active substance. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	17/02/2011	17/02/2011		

	specification parameter to the specification with its corresponding test method B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include:	21/12/2010	n/a	Annex II	

	- a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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 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				
IG/0028	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/11/2010	n/a		
IB/0048/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	24/06/2010	n/a		

	or addition) for the AS or a starting material/intermediate B.III.1.a.1 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IA/0047/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	21/05/2010	21/05/2010	SmPC, Labelling and PL	

	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				
II/0046	Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	19/03/2010	Annex II	
IA/0044	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	27/11/2009	n/a		
II/0042	Change in the manufacturing process of the drug substance Valsartan; addition of an alternative process for the synthesis of one of the compound used. Quality changes	19/11/2009	25/11/2009		
IA/0045	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	25/11/2009	n/a		
IB/0043	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	24/11/2009	n/a	SmPC	
II/0038	To tighthen the specification, modify test procedures and introduce new ones for the active substance	24/09/2009	05/10/2009		

	valsartan in order to update the Testing Monograph of valsartan. Quality changes				
IA/0041	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/08/2009	n/a		
IA/0040	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	28/07/2009	n/a		
IA/0039	IA_09_Deletion of manufacturing site	28/07/2009	n/a		
II/0035	The MAH applied for an update of the SPC section 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 sections 4.3 and 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.
IB/0037	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	13/03/2009	n/a		
IA/0036	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/02/2009	n/a		

II/0031	Update of SPC section 4.8 and PL section 4 regarding the safety information presented for the individual components of the combination product. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	13/02/2009	SmPC and PL	Following the assessment of the 2nd PSUR the CHMP) requested the addition of the terms "myocardial infarction" and "arrhythmia" to SPC section 4.8 with the frequency "not known" because several cases were received during the reporting period of the PSUR and these Adverse Drug Reactions are also seen in connection to the treatment with amlopdipine. Furthermore, additional information regarding the potential decreases in haematocrit and haemoglobin levels for the individual component valsartan was included based on a review which revealed that the information on laboratory evaluation is not in line with monotherapy SPC. The Package Leaflet has been updated to ensure consistency with section 4.8 of the SPC.
IB/0032	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	31/10/2008	n/a		
IA/0034	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	23/10/2008	n/a		
IA/0033	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	23/10/2008	n/a		
IB/0030	IB_33_Minor change in the manufacture of the finished product	25/07/2008	n/a		
IB/0029	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	23/07/2008	n/a		

IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	10/07/2008	n/a		
IA/0027	IA_32_a_Change in batch size of the finished product - up to 10-fold	07/07/2008	n/a		
IB/0025	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	03/07/2008	n/a		
IA/0026	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/06/2008	n/a		
II/0020	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	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 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 9-month

					pregnancy was revised in order to delete the contraindication during the 1st trimester of pregnancy, but to remain the contraindication for the 2nd and 3rd trimester of pregnancy. In addition, a harmonised wording regarding pregnancy across the class was introduced.
IA/0024	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/05/2008	n/a		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/05/2008	n/a	PL	
IA/0023	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	06/05/2008	06/05/2008	SmPC, Labelling and PL	
IA/0022	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	06/05/2008	06/05/2008	SmPC, Labelling and PL	
IA/0021	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	06/05/2008	06/05/2008	SmPC, Labelling and PL	
IB/0017	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	10/12/2007	n/a	SmPC, Labelling and PL	
IA/0016	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	19/09/2007	n/a		
IA/0015	IA_41_a_01_Change in pack size - change in no. of	13/09/2007	13/09/2007	SmPC,	

	units within range of appr. pack size			Labelling and PL	
IA/0014	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0013	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0012	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0011	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0010	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0009	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0008	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IA/0007	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	13/09/2007	13/09/2007	SmPC, Labelling and PL	
IB/0006	IB_14_b_Change in manuf. of active substance	13/07/2007	n/a		

	without Ph. Eur. certificate - new manufacturer				
IA/0004	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	27/04/2007	n/a		
IA/0003	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	02/04/2007	n/a		
IA/0002	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	02/04/2007	n/a		
IA/0001	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	02/04/2007	n/a		