Twynsta

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/0035	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	22/05/2018		SmPC, Labelling and PL	
IB/0033/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	22/03/2018	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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	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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.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) 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)				
PSUSA/180/201704	Periodic Safety Update EU Single assessment - amlodipine / telmisartan	30/11/2017	n/a		PRAC Recommendation - maintenance
IAIN/0031	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/06/2017	31/05/2018	SmPC, Annex II, Labelling and PL	
IAIN/0030/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a	12/12/2016	16/02/2017	Annex II and PL	

	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.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				
IA/0029/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	01/12/2016	n/a		
II/0028	Update of section 4.5 of the SmPC to add safety information regarding concomitant use with the immunosuppressant medicinal products tacrolimus and cyclosporine. In addition, the Marketing Authorisation Holder took the opportunity to correct some editorial mistakes and correct the description of the tablet in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/03/2016	16/02/2017	SmPC and PL	Amlodipine apparently inhibits the cytochrome P450 enzymes CYP3A4 and CYP3A5. Tacrolimus and cyclosporine are immunosuppressive drugs metabolized by the CYP3A enzyme family. Following the review of literature regarding drug-drug interactions between amlodipine and tacrolimus and between amlodipine and cyclosporine, and in line with the agreed wording in the Product Information of other amlodipine-containing medicinal products, it was agreed to update the section 4.5 of Twynsta to include information regarding the risk of concomitant use and monitoring.

R/0026	Renewal of the marketing authorisation.	25/06/2015	20/08/2015	SmPC, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product is adequately demonstrated and therefore considers that the benefit/risk profile of Twynsta remains favourable in the following indication: Treatment of essential hypertension in adults: Add on therapy Twynsta is indicated in adults whose blood pressure is not adequately controlled on amlodipine. Replacement therapy Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Twynsta containing the same component doses The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IA/0027	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	27/05/2015	n/a		
IAIN/0025/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	08/12/2014	n/a		

	(excluding manufacturer for batch release) 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.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.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
IA/0024	A.7 - Administrative change - Deletion of manufacturing sites	08/12/2014	n/a		
IB/0023	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	10/11/2014	n/a		
PSUV/0021	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IA/0022/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	13/10/2014	n/a		
A31/0017	On 17 April 2013, further to the emergence of new evidence from the scientific literature on dual RAS	22/05/2014	04/09/2014	SmPC and PL	For further information please refer to the Renin-angiotensin-system (RAS)-acting agents Article 31

	blockade therapy and given the seriousness of the identified safety concerns, the Italian Medicines Agency (AIFA) initiated a review under Article 31 of Council Directive 2001/83/EC, requesting the Pharmacovigilance Risk Assessment Committee (PRAC) to issue a recommendation on the benefit-risk of dual RAS blockade therapy through the combined use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs) or aliskiren and to determine whether any regulatory measures should be taken on the marketing authorisations of the products involved in this procedure.				referral - Assessment report.
IA/0019	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	28/04/2014	n/a		
IG/0432	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	16/04/2014	n/a		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/2013	04/09/2014	PL	
WS/0362	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/04/2013	12/08/2013	SmPC, Annex II, Labelling	For Micardis, Micardis Plus, Kinzalmono, kinzalkomb, Pritor, Pritor Plus Update of sections 4.2, 4.3, 4.4 and 4.5 of the SmPC to

	The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH			and PL	implement recommendations regarding the use of telmisartan with aliskiren as requested by the CHMP in the PSUR following the outcome of Article 20 related to aliskiren. In addition, information related to interaction with digoxin is added in section 4.5 of the SmPC. The Package leaflet is updated accordingly. Furthermore, the WSA took the opportunity to sort out a number of inconsistencies in content between SmPCs and PILs for the different products as follows: For Micardis, Micardis Plus, Kinzalmono, kinzalkomb, Pritor, Pritor Plus - Inconsistency between SmPC section 4.5 and PIL regarding interaction with alcohol, barbiturates, narcotics or antidepressants - Inconsistency between SmPC section 4.2 and PIL regarding the storage recommendation. For Twynsta, Onduarp PIL section 4 will be brought in line with SmPC section 4.8 with regard to the side effect hyperglycaemia (amlodipine component) For Micardis Plus, Kinzalkomb, Pritor Plus In the PIL section 2, there is a different wording of telmisartan mono products compared to the telmisartan/HCTZ products for the explanation of cholestasis or biliary obstruction. The MAH proposes to align the wording in the PIL of the telmisartan/HCTZ products so that it is identical with telmisartan mono products. Besides, editorial changes are proposed for Twynsta, Onduarp, Micardis, MicardisPlus, Pritor, PritorPlus,

					Kinzalmono and Kinzalkomb regarding storage recommendations in Annex IIIA in bold characters to bring them in line with the printing style on the actual, marketed products. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Micardis and Micardis Plus: (Belgium, Bulgaria and Luxembourg, Estonia, Lithuania) Twynsta/Onduarp (Estonia, Belgium and Luxembourg) Furthermore, the WSA proposed this opportunity to bring the PI in line with the latest QRD template (Version 9).
WS/0320	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 product - Other variation	15/11/2012	15/11/2012		
WS/0283	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 in order to include a statement on a drug-drug interaction between amlodipine and simvastatin when used concomitantly. Section 2 of the Package Leaflet is updated accordingly. In addition the MAH has taken the opportunity to make a correction on the 360 tablets multipack in section 6 of the PIL for Twynsta and Onduarp and in Annex A for	20/09/2012	25/10/2012	SmPC and PL	This type II variation concerns an update of section 4.5 the SmPC to include a new drug-drug interaction between amlodipine and simvastatin. When used concomitantly with amlodipine, the maximum daily dose of simvastatin should not exceed 20 mg.

	Twynsta only. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
WS/0236	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update to section 4.4 of the SmPC to include a warning for diabetic patients when treated with insulin or oral antidiabetics and to include a warning on RAAS blockage in patients with uncontrolled blood pressure. Furthermore the MAH has corrected the visual description of the appearance of the product in section 3 of the SmPC and section 6 of the PL. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8. Finally the MAH took the opportunity to make some editorial changes in the English Annexes, to make some corrections in the DE, FR, IT, LV, NL and SK Annexes for Onduarp, in the DE, FR, IT, LV, NL and SK Annexes for Twynsta. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SmPC, Annex II, Labelling and PL	This type II variation concerns an update of section 4.4 the SmPC to include a warning for diabetic patients when treated with insulin or oral antidiabetics and to include a warning on RAAS blockage in patients with uncontrolled blood pressure, in line with the telmisartan SmPC.

WS/0255/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 the Description of Pharmacovigilance System (DDPS). C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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.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	24/05/2012	24/05/2012		Changes to an existing pharmacovigilance system as described in the DDPS. The MAH update the Detailed Description of the Pharmacovigilance System (DDPS) for Aptivus, MicardisPlus, Mirapexin, Onduarp, Pradaxa, Sifrol, Trajenta, Twynsta and Viramune.
IG/0165	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	10/04/2012	n/a		

IB/0008/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.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	15/11/2011	n/a		
IB/0007/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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	15/11/2011	n/a		

IB/0006	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	04/07/2011	n/a	SmPC	
II/0004	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.5 of the Summary of Product Characteristics regarding an interaction between amlodipine and grapefruit. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	14/06/2011	SmPC and PL	In this type II variation application (C.I.4), the MAH has updated section 4.5 of the Twynsta Summary of Product Characteristics (SmPC) regarding an interaction between amlodipine and grapefruit, in line with the Norvasc's SmPC (originator for Amlodipine). Consequential changes to the Package Leaflet have been made. The available data are consistent with the assumption that the potential interaction between amlodipine and grapefruit juice may be less pronounced than with other calcium channel blockers. The point estimate for changes in AUC and Cmax values were between 107 and 116% in the published studies. There were no significant changes in blood pressure values in healthy volunteers when concomitant intake of grapefruit juice was compared to concomitant intake of water. Minor differences were observed in standing pulse. Considering the interindividual differences in bioavailability and the lack of data in patients with arterial hypertension the conclusions of the MAH are shared by the CHMP. At present it cannot be excluded that the mild increase in bioavailability is of clinical relevance for individual patients. Therefore, the proposed changes in the Twynsta SmPC and Package Leaflet are supported by the CHMP.
II/0003	Update of section 4.6 of the Summary of Product Characteristics to include information regarding the effects of telmisartan and amlodipine on fertility and update of section 5.3 to include further information regarding effects on postnatal development.	14/04/2011	14/06/2011	SmPC	In this type II variation application (C.I.4), the MAH has submitted proposed changes to section 4.6 and 5.3 of the Twynsta Summary of Product Characteristics (SmPC) to align it with version 7.3.1 of the QRD template and with the new SmPC Guideline. Section 4.6 has been amended to reflect

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				that there are no effects of telmisartan and amlodipine on male and female fertility. In addition, a statement has been included to inform the prescribers that separate reproductive toxicity studies assessing the potential effects of telmisartan and amlodipine on male or female fertility when both compounds are used in combination have not been conducted. Section 5.3 has been amended to align it with the Micardis (telmisartan) SmPC. The CHMP agreed with the changes to the SmPC requested by the MAH as part of this variation.
II/0002	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet Update of section 4.8 of the Summary of Product Characteristics to add the adverse drug reaction (ADR) 'hypoglycaemia' as well as further information regarding the already listed ADRs 'angioedema' and 'liver disorder' and to delete the ARDs "paraesthesia" and "peripheral neuropathy". The Package Leaflet has been updated accordingly. The MAH took the opportunity to delete the version number of the DDPS in Annex II and has also made editorial changes throughout the Annexes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	14/06/2011	SmPC, Annex II, Labelling and PL	In this type II variation application (C.I.4), the MAH submitted new safety findings associated with the use of Twynsta or one of its components related to hypoglycaemia, abnormal hepatic function/liver disorder, potential fatal outcome of angioedema, and proposed to delete paresthesia and peripheral neuropathy as these adverse drugs reactions are mentioned twice in the Summary of Product Characteristics (SmPC). Consequently, sections 4.8 of the SmPC and section 4 of the Package leaflet have been updated. The MAH also took the opportunity to delete the version number of the DDPS from Annex II and to make editorial changes throughout the Annexes. The CHMP agreed with the changes to the SmPC, Annex II and the Package Leaflet requested by the MAH as part of this variation.
IA/0005	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	04/05/2011	n/a		

IA/0001/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/12/2010	n/a		