EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pelzont

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
A20/0038	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 19 December 2012, the opinion of the CHMP on whether the marketing authorisation should be maintained, varied, suspended or withdrawn.	10/01/2013	22/03/2013		Please refer to the Assessment Report: H-903-AR-A20-0038-en
WS/0301	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/09/2012	29/10/2012	SmPC, Labelling and	During the assessment of PSUR No. 7 for Tredaptive covering the period 9 May 2010 to 8 November 2011 changes to section 4.8 of the EU SmPC were requested by

[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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	This type II variation concerns the amendment of section 4.8 of the SmPC in accordance with the QRD template as per the CHMP request included in the Assessment Report on the PSUR 7 for Tredaptive/Trevaclyn/Pelzont. The Patient Leaflet, section 4, was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in Sweden and Malta in the Package Leaflet. The format of the numbers used to express the strength of Tredaptive/Trevaclyn/Pelzont on blister foil was amended in order to improve clarity. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH			PL	the CHMP. These updates are necessary to bring the PI in line with the SmPC guideline requirement and the valid QRD template. Thus, the type II variation concerns the amendment of section 4.8 of the SmPC in accordance with the QRD template. The Patient Leaflet, section 4, was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in Sweden and Malta in the Package Leaflet. The format of the numbers used to express the strength of Tredaptive/Trevaclyn/Pelzont on blister foil was amended in order to improve clarity.
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
WS/0217	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type II variation concerns an update of section 5.1 of the SmPC based on the results of the withdrawal study (P102). Further, for completeness and consistency with the information already provided in section 4.4 of the SmPC, the MAH proposes to update also SmPC section 5.2 with recommendations	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	This variation involved amendment of the PI with new information that became available after the completion of study P102. This study demonstrated the value of laropiprant to reduce moderate or greater flushing past 6 months. Specifically, dyslipidaemic patients in whom laropiprant was withdrawn after 20 weeks on Tredaptive experienced significantly more flushing than patients who continued taking Tredaptive in terms of number of days per week with moderate or greater flushing. The incidence and frequency of moderate or greater flushing in patients

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	regarding co-administration with simvastatin in Chinese patients. In addition, the MAH took the opportunity to update the annexes in line with the latest version of the QRD template (version 8) and to update the list of local representatives (Portugal, the Netherlands, Iceland, Hungary and Italy) 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				treated with Tredaptive for the duration of the study decreased. Further update concerned the repetition of the information on "Race" agreed in previous procedure for section 4.4 of the SmPC and adding in section 5.2.
IG/0152/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.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) A.7 - Administrative change - Deletion of manufacturing sites	15/03/2012	n/a		
IG/0112	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.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	11/10/2011	n/a		

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WS/0154	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change in the specification parameters and limits of an excipient. B.II.c.1.f - Change in the specification parameters and/or limits of an excipient - Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue	22/09/2011	22/09/2011		
WS/0123	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics and Package Leaflet C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	24/08/2011	SmPC, Annex II and PL	This type II variation work-sharing is being submitted to propose changes to section 4.5 of the SmPC, subsection "Acetylsalicylic acid and clopidogrel", related to the potential for pharmacodynamic interactions for MK-0524A in patients taking aspirin and clopidogrel together. The variation is based on the results of study P114, which evaluated the effects of laropiprant on platelet function in subjects concomitantly administered both aspirin and clopidogrel. P114 was a follow-up study to P072 Part II that was previously conducted but was inconclusive. In addition, the list of local representatives in section 6 of the Patient Leaflet has been updated. Annex II was aligned with the appropriate wording on Risk Management Plan. This application was submitted for a group of variations consisting of a Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
IG/0086	B.III.1.a.2 - Submission of a new or updated Ph. Eur.	05/08/2011	n/a		

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	Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
WS/0118	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II and 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	14/04/2011	18/05/2011	SmPC and PL	This work sharing type II variation concerns an update of section 4.8 of the SmPC to include the ADR 'vesiculobullous rash'. The PI was amended accordingly. In addition, the MAH took the opportunity to update the contact details in the list of local representatives in the Package Leaflet for the UK and the Netherlands. This application was submitted for a group of variations consisting of a Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The MAH conducted a search in the WAES database for spontaneous reports with the MedDRA PTs of blister and dermatitis bullous in patients on therapy with ER niacin/laropiprant from market introduction till November 2010. Thirteen postmarketing reports (1 serious, 12 nonserious) and 1 serious study report were identified. This resulted in an update of the SmPC and the term "vesiculobullous rash" has been added in section 4.8. This is also reflected in the Package Leaflet under the term "blistering rash". The benefit-risk ratio of the medicinal products remains favourable.
IB/0023	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	12/05/2011	n/a	SmPC, Labelling and PL	
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/04/2011	n/a	PL	

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WS/0058	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To reduce the shelf life of the finished product packaged in aluminium/aluminium blisters from 24 to 18 months. B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	16/12/2010	24/01/2011	SmPC	
WS/0054	This was an application for a variation 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 SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC	This type II variation concerns an update of sections 4.6 and 5.3 of the SPC to include nicotinic acid data from the developmental and reproductive toxicology (DART) studies. No nicotinic acid-related adverse effects on fertility were observed in male and female rats up to exposure levels approximately 391 times the human AUC of nicotinic acid based on the AUC of the recommended daily human dose. Nicotinic acid was not teratogenic in rats and rabbits up to exposure levels approximately 253 and 104 times the human AUC of nicotinic at the recommended daily human dose, respectively. In rats, foetotoxic effects (significantly decreased foetal body weights associated with a decrease in the number of ossified sacrocaudal vertebrae and an increased incidence of foetuses with sites of incomplete ossification) were noted in the absence of any signs of maternal toxicity at exposure levels approximately 959 times the human AUC of nicotinic acid at the recommended daily human dose. Similar treatment-related changes were observed in rabbit foetuses but in the

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					presence of maternal toxicity at exposure levels approximately 629 times the human AUC of nicotinic acid at the recommended daily human dose. This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
WS/0060	This was an application for a variation 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 SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC, Annex II and PI	This type II variation concerns an update of section 4.8 of the SPC to include the ADR 'anaphylactic shock' based on post-marketing experience in patients on therapy with ER niacin/laropiprant. Section 4 of the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the SPC and Package Leaflet in line with the latest QRD templates (version 7.3.1) and the latest SPC guideline, and to make minor editorial changes in the annexes as well as to update the contact details in the list of local representatives in the Package Leaflet for Cyprus and Malta. This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Anaphylactic shock: Section 4.8 of the SPC currently includes 'angioedema' and 'Type I hypersensitivity'. However, the most severe expression of anaphylaxis, anaphylactic shock, has so far not been identified in the current product information. A review of one post-marketing report of anaphylactic shock cannot exclude the possibility of a causal association. As a result, the term "anaphylactic shock" has been added in section 4.8 as an adverse experience reported in post-marketing use. The MAH will continue to monitor reports of anaphylactic shock

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					in patients who are treated with ER niacin/laropiprant as part of routine pharmacovigilance activities.
IG/0027	This was an application for a group of variations. C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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	10/11/2010	n/a	Annex II	
II/0019	Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	25/01/2010	SmPC and PL	
IA/0020	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	14/01/2010	n/a		
II/0017	Introduction of several changes relation to laropiprant (the active substance). Change(s) to the test method(s) and/or specifications for the active substance	19/11/2009	25/11/2009		
II/0018	Introduction of several changes relation to Niacin (the active substance). Change(s) to the test method(s) and/or specifications for the active substance	19/11/2009	25/11/2009		
II/0014	Changes relating to manufacturers of laropiprant (the active substance) which include:	22/10/2009	27/10/2009		

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	- change in the name of the approved manufacturer, - addition of an alternative manufacturer of laropiprant. - change in the name and address of the approved manufacturer of the starting material used in manufacturing process of laropiprant. Quality changes				
IB/0015	IB_33_Minor change in the manufacture of the finished product	04/09/2009	n/a		
II/0008	Update of Summary of Product Characteristics	23/07/2009	28/08/2009	SmPC and PL	The following amendments (underlined text) are introduced in Section 4.5 of the SPC: Clopidogrel: In a clinical study, there was no meaningful effect of laropiprant on the inhibition of ADP induced platelet aggregation by clopidogrel, but there was a modest increase in the inhibition of collagen induced platelet aggregation by clopidogrel. The clinical significance of these observations is unknown. This effect is unlikely to be clinically important as laropiprant did not increase bleeding time when coadministered with clopidogrel throughout the dosing interval. " Acetylsalicylic acid and clopidogrel: A clinical study to evaluate the effect of laropiprant on platelet function in patients concomitantly receiving both acetylsalicylic acid and clopidogrel was inconclusive. Because this study did not rule out the potential for prolongation of bleeding time, patients receiving Tredaptive concomitantly with acetylsalicylic acid and clopidogrel should be closely

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					monitored.
II/0007	Update of DDPS (Pharmacovigilance)	25/06/2009	06/08/2009	Annex II and PL	The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements and is considered acceptable. Consequently, Annex II has been updated with the new version number of the agreed DDPS (version 6.0). Details of the local representative for Malta in the Package Leaflet were also updated.
IA/0009	IA_13_a_Change in test proc. for active substance - minor change	29/06/2009	n/a		
IA/0010	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	29/06/2009	n/a		
IA/0011	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	29/06/2009	n/a		
IA/0012	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	29/06/2009	n/a		
IA/0013	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	29/06/2009	n/a		
II/0006	Change to the specification limit of dissolution method for the finished product. Change(s) to the test method(s) and/or specifications for the finished product	23/04/2009	29/04/2009		
IB/0005	IB_33_Minor change in the manufacture of the finished product	19/02/2009	n/a		

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IA/0003	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	18/12/2008	18/12/2008	SmPC, Labelling and PL	
IA/0004	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	18/12/2008	18/12/2008	SmPC, Labelling and PL	
IA/0002	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	02/10/2008	02/10/2008	SmPC, Labelling and PL	The Marketing Authorisation Holder applied for the addition of a new pack size of 196 tablets (2 cartons of 98 tablets).

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