EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ipreziv

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
A31/0006	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	22/05/2014	09/09/2014	SmPC and PL	For further information please refer to the Renin-angiotensin-system (RAS)-acting agents Article 31 referral - Assessment report.

[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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	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.				
T/0012	Transfer of Marketing Authorisation	07/04/2014	22/05/2014	SmPC, Labelling and PL	Transfer of the Marketing Authorisation to Takeda Pharma A/S.
PSUV/0010	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
IG/0408/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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	24/02/2014	22/05/2014	SmPC, Labelling and PL	
WS/0464/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 a new supplier of an starting material. - To add a new supplier of an starting material. - Change in the manufacturing process of the active substance. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	18/12/2013	n/a		

	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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
PSUV/0008	Periodic Safety Update	19/09/2013	11/11/2013	SmPC	For further information please refer to: Ipreziv-H-2517-Grounds-PSUV-08-en.
WS/0405	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3, 4.4, 4.5, and 4.8 of the SmPC, as per the PRAC/CHMP request set out in the PRAC PSUR Assessment Report dated 7 March 2013, in order to: - include relevant contraindications and warnings regarding concomitant use of azilsartan medoxomil and aliskiren (section 4.3, 4.4 and 4.5); - include the adverse drug reactions 'rash', 'pruritus', 'nausea' and 'muscle spasm' with the frequency 'uncommon' (section 4.8). The Package Leaflet is 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	19/09/2013	11/11/2013	SmPC, Annex II and PL	The MAH was requested in the conclusions of the final PRAC PSUR assessment report (AR) covering the period 25 February 2012 to 24 August 2012 (EMEA/H/C/002293/PSU 003 and EMEA/H/C/002517/PSU 003) to submit a Type II variation in order to include relevant contraindications and warnings regarding concomitant use of azilsartan medoxomil and aliskiren. A few published studies building upon the preliminary results of the ALTITUDE study which raised safety concerns regarding dual renin-angiotensin system (RAAS) blockade when aliskiren was co-administered with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in patients with Type II diabetes mellitus and renal impairment, was the evidence that supported the PRAC request. To be noted that azilsartan medoxomil is an angiotensin II receptor blocker (ARB), indicated for the treatment of essential hypertension in adults. The preliminary results of ALTITUDE study were assessed by the CHMP as part of an Article 20 of Regulation (EC) No 726/2004Article referral procedure (EMEA/H/C/000780/A-20/0063) initiated by the EC covering all aliskiren containing products. The CHMP opinion was issued in February 2012. At that time, based on the available

					data, the CHMP decided that the contra-indication for concomitant use of the ARBs and aliskiren should be extended to patients with moderate renal impairment (defined as patients with GFR < 60 mL/min/1.73m2) in addition to diabetic patients. No other direct evidence of such interactions (with aslikiren) in patients exposed to azilsartan medoxomil is available in the MAH's safety database. Therefore the CHMP considered that based on the available evidence it is appropriate to include contraindications and warnings regarding concomitant use of azilsartan medoxomil and aliskiren. Conseqeuntly the SmPC section 4.3, 4.4 and 4.5 were updated accordingly. Furthermore, based on the conclusions of the PRAC AR on the responses to the request for additional information set out in the above mentioned PSUR procedures (LEG 003.1), the MAH proposed to include the side effects 'rash', 'pruritus', 'nausea' and 'muscle spasm' in section 4.8 of the SmPC. The PL was proposed to be updated accordingly. Based on the submitted data and according to the PRAC assessment and conclusions, which indicated that a causality relationship was established between the mentioned side effects and the use of azilsartan medoxomil, the CHMP endorsed the MAH proposal to include the side effects 'rash', 'pruritus' under 'Skin and subcutaneous tissue disorders' system organ class (SOC), 'nausea' under 'Gastrointestinal disorders' SOC and 'muscle spasm' under 'Musculoskeletal and connective tissue disorders' SOC in section 4.8 of the SmPC. It was considered that the proposed frequency,' uncommon', appropriately reflects the reported frequency. The Package Leaflet was updated accordingly.
IG/0347	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of	09/09/2013	n/a		

	the AS				
IG/0285	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/04/2013	n/a		
IG/0231	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	n/a		
IG/0164/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. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	20/04/2012	n/a	SmPC, Labelling and PL	

IB/0001/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside 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	20/04/2012	n/a	SmPC, Labelling and PL	