Edarbi

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
II/0031	Please refer to the Recommendations section B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant	14/07/2022	n/a		Not applicable.

[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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	update to the relevant AS section in the dossier				
II/0030/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/02/2022		SmPC, Labelling and PL	
PSUSA/280/202008	Periodic Safety Update EU Single assessment - azilsartan medoxomil, azilsartan medoxomil/chlortalidone	09/04/2021	n/a		PRAC Recommendation - maintenance
IB/0029/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation A.1 - Administrative change - Change in the name and/or address of the MAH	19/01/2021	03/02/2022	SmPC, Annex II, Labelling and PL	
IA/0027	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	29/06/2020	n/a		

	size				
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/01/2020	03/02/2022	PL	
IB/0025	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/07/2019	n/a		
IA/0024	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	11/12/2018	n/a		
IA/0023	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	20/06/2018	n/a		
II/0021	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2018	n/a		
PSUSA/280/201708	Periodic Safety Update EU Single assessment - azilsartan medoxomil, azilsartan medoxomil/chlortalidone	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0022/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms	20/03/2018	25/03/2019	SmPC, Labelling and PL	

	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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				

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IB/0019/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 or intermediate product - Minor change in the manufacturing process	11/07/2017	n/a		
R/0018	Renewal of the marketing authorisation.	15/09/2016	14/11/2016	SmPC, Annex II, Labelling and PL	

IG/0652	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	22/01/2016	n/a		
IB/0016	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	24/11/2015	n/a		
PSUSA/280/201408	Periodic Safety Update EU Single assessment - azilsartan medoxomil, azilsartan medoxomil/chlortalidone	12/03/2015	n/a		PRAC Recommendation - maintenance
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/12/2014	n/a		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2014	14/11/2016	PL	
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 use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor	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.

	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	06/06/2014	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	06/06/2014	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.	18/12/2013	n/a		

	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.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	In the current Summary of Product Characteristics (SmPC) the following statement is included below the adverse drug reactions (ADR) table in section 4.8: 'Angioedema, including circumoral oedema and periorbital oedema, was rarely seen in patients during open label treatment with Edarbi/Ipreziv'. Based on the fact that angioedema is a well-known class effect of Angiotensin II Receptor Blockers (ARBs), angioedema has been reported for azilsartan and has been assessed as being related to azilsartan medoxomil the PRAC considers that the adverse drug reaction 'angioedema' should be included in the ADR table (SmPC section 4.8) under the system organ class (SOC) 'Skin and subcutaneous disorders'. In addition the frequency 'rare' should be assigned based on a single case observed in a subject exposed to azilsartan medoxomil during the clinical trial program.
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	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

	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				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 the AS	09/09/2013	n/a		
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	20/04/2012	12/07/2012	SmPC, Labelling and	

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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.	20/04/2012	12/07/2012	SmPC, Labelling and PL	

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