EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Libertek

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
T/0031	Application for Transfer of Marketing Authorisation from Takeda GmbH to AstraZeneca AB. Transfer of Marketing Authorisation	14/10/2016	03/11/2016	SmPC, Labelling and PL	
WS/1037	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	13/10/2016	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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	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/2658/201601	Periodic Safety Update EU Single assessment - ROFLUMILAST	02/09/2016	n/a		PRAC Recommendation - maintenance
IG/0699	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	04/07/2016	n/a		
IG/0691/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.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	26/05/2016	n/a		
WS/0924	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	01/04/2016	n/a		
IG/0657	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	25/01/2016	n/a		

	location				
WS/0768	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 4.4, 4.8, 5.1 and 5.2 5.1 of the SmPC in order to amend the safety information based on completion of Clinical Study RO-2455-404-RD ("REACT"). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	03/11/2016	SmPC	This procedure amend sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety information based on completion of Clinical Study RO-2455-404-RD ("REACT"). The REACT study was a randomized, double-blind, parallel-group, multicenter, placebo controlled phase 3b/4 study performed to investigate the efficacy and safety of roflumilast on top of a fixed dose of long-acting Beta 2-agonists (LABAs) and inhaled corticosteroids (ICS) in patients with severe COPD. Results indicate that treatment with roflumilast may lead to a higher risk of sleep disorders (mainly insomnia) in patients with a baseline body weight of <60 kg, due to a higher total PDE4 inhibitory activity found in these patients.
T/0024	Transfer of Marketing Authorisation from Takeda GmbH to Takeda GmbH. Transfer of Marketing Authorisation	23/09/2015	28/10/2015		Transfer of Marketing Authorisation from Takeda GmbH to Takeda GmbH.
PSUSA/2658/ 201501	Periodic Safety Update EU Single assessment - ROFLUMILAST	09/07/2015	n/a		PRAC Recommendation - maintenance
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/06/2015	28/10/2015	PL	
R/0020	Renewal of the marketing authorisation.	26/02/2015	24/04/2015	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 continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Libertek continues to be favourable. The CHMP is of the opinion that an additional five-year

					renewal on the basis of pharmacovigilance grounds is required.
PSUSA/2658/201407	Periodic Safety Update EU Single assessment - ROFLUMILAST	22/01/2015	23/03/2015	SmPC and PL	Please refer to roflumilast EMEA/H/C/PSUSA/2658/201407 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IG/0470	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	15/08/2014	n/a		
PSUV/0016	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
IG/0406	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	07/02/2014	n/a		
PSUV/0014	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IG/0353	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	20/09/2013	01/09/2014	SmPC, Annex II, Labelling and PL	
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/08/2013	01/09/2014	PL	Update of the local representative's contact details for France and inclusion of an additional local representative of the MAH for the new Member State, Croatia.
WS/0352	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	21/02/2013	26/03/2013	SmPC, Annex II, Labelling and PL	A cumulative review of adverse drug reactions (ADR) reports of angioedema received in the framework of post-marketing surveillance since market introduction of roflumilast (05 July 2010 – 05 July 2012) revealed a total of 55 medically

	Addition of 'angioedema' as undesirable effect in section 4.8 of the SmPC with frequency 'rare' as requested by the CHMP following the assessment of PSUR 3. The Package Leaflet was updated accordingly. Additionally, the information regarding allergic reactions in section 4 of the PL was updated in accordance with the review of cumulative cases reported. Changes were also made to the PI to bring it in line with the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				confirmed and non-medically confirmed cases reporting terms potentially suggestive of angioedema. Thirteen of these reports were serious, all of which were reported spontaneously. A total of 42 non-serious reports have been received to date; seventeen were reported from studies and the remainder were spontaneous reports. Five of the serious cases reported the term angioedema, 4 reported face swelling and there were two reports of tongue swelling. Of the non-serious cases, 5 reported the event face swelling, 4 reported the event of swollen tongue, 3 reported eye/eyelid swelling and there were two reports of lip swelling and pharyngeal oedema respectively. There have been single non serious reports of angioedema, oropharyngeal swelling and mouth oedema. Despite the absence of a clear pharmacological pathogenesis, based on this cumulative review, angioedema may be associated with the use of roflumilast. Key factors supporting this conclusion include: 1 case with a possible positive rechallenge, 5 cases with a possible positive dechallenge and 9 cases with a plausible temporal relationship. Although these reports provided limited information, the overall body of evidence supports an association between roflumilast and angioedema. It is therefore recommended that angioedema be included as an ADR in the roflumilast PI.
IG/0289	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/03/2013	n/a		
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2013	26/03/2013	PL	
IG/0262/G	This was an application for a group of variations.	25/01/2013	26/03/2013	SmPC, Annex	

	A.1 - Administrative change - Change in the name and/or address of the MAH 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.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release			II, Labelling and PL	
IG/0245	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/12/2012	n/a		
WS/0231	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 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) of roflumilast regarding the risk of psychiatric disorders in line with the available post-marketing data as requested by the CHMP following the assessment of the 2nd PSUR. Annex II and sections 2 and 4 of the Package Leaflet have been updated accordingly and the list of local representatives has been updated. 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	20/09/2012	24/10/2012	SmPC, Annex II and PL	In the reporting period of PSUR 2 for roflumilast (6 January 2011 – 5 July 2011), more than 26% of the ADRs reported were serious. Among these more than 26% reported an ADR related to a potentially risk of triggering suicide (suicidal ideation (17), attempt suicide (2), completed suicide (2)), and more than 40% reported an ADR related to depression (depression (16), depressed mode (2), anxiety (8), insomnia (4), nervousness (4)). During the reporting period, of the seventeen (17) cases of suicidal ideation, seven (7) occurred rapidly, already on the day of the start of treatment with roflumilast or within the first week of treatment. In eight (8) reports, time to onset, ranged between 10 days and 2.5 month and in two (2) reports the time to onset was unknown but reported rechallenge positive. Among these seventeen (17) cases, eight (8) reports presented a medical history of psychiatric problems related to depression, anxiety and panic disorders, alcohol problems

	MAH				and anorexia and six (6) reports no presented previous history of depression Despite the high prevalence and incidence of depression in patients with severe COPD, a causal relationship between roflumilast and suicidal ideation or behaviour can't be excluded. According to the post-marketing experience, suicidal ideation could appear in patients without a previous history of depression and the time to onset could range between one day and several weeks. In addition, medical history of psychiatric problems such as anxiety, panic disorders, anorexia and alcoholism, among others, could be risk factors of these ADR on suicidal ideation.
IG/0215	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/08/2012	n/a		
IG/0084	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	29/06/2011	n/a		
IG/0083/G	This was an application for a group of variations. 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	29/06/2011	n/a		
IB/0001	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	25/05/2011	n/a	SmPC, Labelling and	

	(supported by real time data)			PL	