Daxas

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
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/08/2022		PL	
IA/0046	A.7 - Administrative change - Deletion of manufacturing sites	04/07/2022	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).

IB/0045	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/05/2022		Annex II	
IB/0044	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/09/2021		Annex II and PL	
PSUSA/2658/ 202101	Periodic Safety Update EU Single assessment - roflumilast	02/09/2021	n/a		PRAC Recommendation - maintenance
IB/0042	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/11/2020	06/05/2021	Annex II	
IB/0041/G	This was an application for a group of variations. B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement B.II.b.1.a - Replacement or addition of a 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.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	04/09/2020	06/05/2021	SmPC, Annex II, Labelling and PL	

	packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IA/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/05/2020	06/05/2021	SmPC	
R/0039	Renewal of the marketing authorisation.	26/03/2020	20/05/2020	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Daxas in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. In addition, the SmPC and Package leaflet were updated in line with the latest QRD template.

II/0038	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	16/01/2020	20/05/2020	SmPC, Annex II and PL	Following a request from PRAC, the MAH submitted this type II variation to implement changes related to reclassification and removal of safety concerns as well as reviewing the need of additional Risk Minimisation Measures. The important identified risk: Angioedema, the important potential risks: gynecomastia, pancreatitis, persistent intolerability in high-exposure populations, off-label use and the missing information: intake of immunosuppressive medications, severe immunological diseases, mild, moderate or sever hepatic impairment, combination of roflumilast with theophylline for maintenance therapy and use during pregnancy and lactation have been removed. These changes are endorsed but pancreatitis and patients with mild hepatic impairment classified as Child Pugh A should continue to be closely monitored in the next PSURs. Serious diarrhoea has been upgraded as an important idenfied risk. The important identified risk psychiatric disorders (insomnia, anxiety, panic attack, nervousness, depression, suicidal ideation and behaviour) and the important potential risk of triggering suicide remain unchanged, the proposal of the MAH to merge both risks was not endorsed. Of note, one of the secondary objective of the PASS category 1 is to compare the incidences of death by suicide or hospitalisation for suicide attempt, between roflumilast treated COPD patients and COPD patients not treated with roflumilast Therefore, an additional pharmacovigilance activity is ongoing for this safety concern. The important potential risks infections and cardiac safety have been renamed as lower respiratory tract infections and major cardiovascular events respectively. However,

					new diagnosis of tuberculosis or hepatitis B or C or other severe viral hepatitis infection are endpoints of the PASS category 1 which is ongoing for Roflumilast and therefore the PRAC requested that the risk of infections remains unchanged as an important potential risk. Based on the post-marketing data and post marketing experience gained, the PRAC considered that additional Risk Minimisation Measures in place are no longer needed. They have therefore been removed from the RMP.
PSUSA/2658/ 201801	Periodic Safety Update EU Single assessment - roflumilast	12/07/2018	n/a		PRAC Recommendation - maintenance
X/0035	Annex I_2.(c) Change or addition of a new strength/potency	22/02/2018	23/04/2018	SmPC, Labelling and PL	
PSUSA/2658/ 201701	Periodic Safety Update EU Single assessment - roflumilast	01/09/2017	n/a		PRAC Recommendation - maintenance
T/0034	Application for Transfer of Marketing Authorisation from Takeda GmbH to AstraZeneca AB. Transfer of Marketing Authorisation	14/10/2016	18/11/2016	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. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/10/2016	n/a		

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 location	25/01/2016	n/a		

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	18/11/2016	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/0027	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
R/0024	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 Daxas 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/	Periodic Safety Update EU Single assessment -	22/01/2015	08/04/2015	SmPC and PL	Please refer to roflumilast EMEA/H/C/PSUSA/2658/201407

201407	roflumilast				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/0020	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/0018	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/0016	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. Addition of 'angioedema' as undesirable effect in section 4.8 of the SmPC with frequency 'rare' as	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 confirmed and non-medically confirmed cases reporting terms potentially suggestive of

	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				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/0014	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 II, Labelling	

	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			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 -	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

	Change(s) with new additional data submitted by the MAH				to depression, anxiety and panic disorders, alcohol problems 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		
N/0009	Amendment of the United Kingdom local representative's contact details in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/02/2012	24/11/2012	PL	
N/0007	Update of the local representatives contact details in the Package Leaflet for Germany, Romania, Slovenia, Sweden and the United Kingdom." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2012	24/11/2012	PL	

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/0003/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.2 - Change in pack size of the finished product - Change in the number of units (e.g.	02/05/2011	02/05/2011	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes				
IB/0002	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)	28/03/2011	n/a	SmPC, Annex II and Labelling	
N/0001	Update of the German and UK local representatives' contact details. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/09/2010	n/a	PL	