Rilutek

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/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2024		PL	
PSUSA/2645/ 202312	Periodic Safety Update EU Single assessment - riluzole	11/07/2024	n/a		PRAC Recommendation - maintenance

[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).

N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/01/2024		PL	
T/0072	Transfer of Marketing Authorisation	12/10/2023	15/11/2023	SmPC, Labelling and PL	
PSUSA/2645/ 202112	Periodic Safety Update EU Single assessment - riluzole	15/09/2022	09/11/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2645/202112.
IA/0070	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	14/12/2021	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/11/2021	09/11/2022	PL	
IG/1386	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	03/08/2021	15/11/2021	Annex II and PL	
IA/0067	A.7 - Administrative change - Deletion of manufacturing sites	06/04/2021	n/a		
WS/1829	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2020	15/11/2021	SmPC, Annex II and PL	

II/0065	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 update to the relevant AS section in the dossier	06/11/2020	n/a		
IA/0066/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/07/2020	n/a		
PSUSA/2645/ 201912	Periodic Safety Update EU Single assessment - riluzole	09/07/2020	n/a		PRAC Recommendation - maintenance
IB/0062	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	10/12/2019	n/a		
IA/0061	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2019	n/a		
IAIN/0060	A.1 - Administrative change - Change in the name and/or address of the MAH	14/08/2019	27/07/2020	SmPC, Labelling and	

				PL	
T/0059	Transfer of Marketing Authorisation	05/04/2019	06/06/2019	SmPC, Labelling and PL	
PSUSA/2645/ 201712	Periodic Safety Update EU Single assessment - riluzole	12/07/2018	n/a		PRAC Recommendation - maintenance
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2017	06/06/2019	Labelling and PL	
PSUSA/2645/ 201512	Periodic Safety Update EU Single assessment - riluzole	02/09/2016	n/a		PRAC Recommendation - maintenance
N/0056	Update of the package leaflet with revised contact details of the local representatives for Hungary, Italy and Lithuania. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/03/2016	06/06/2019	PL	
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/11/2015	06/06/2019	PL	
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/07/2015	06/06/2019	PL	
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/11/2014	19/12/2014	PL	
PSUSA/2645/ 201312	Periodic Safety Update EU Single assessment - riluzole	11/09/2014	n/a		PRAC Recommendation - maintenance

IA/0051	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/08/2014	n/a		
IAIN/0050	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	05/08/2014	n/a		
IG/0454	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	17/07/2014	n/a		
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/03/2014	19/12/2014	PL	
IB/0046	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/12/2013	19/12/2014	SmPC, Annex II, Labelling and PL	
IA/0045/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	18/11/2013	n/a		

IG/0313	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/06/2013	n/a		
IB/0043	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	15/01/2013	n/a		
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/2012	19/12/2014	PL	
IB/0041/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	05/06/2012	n/a		
IB/0040	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	07/06/2011	n/a		
IA/0039/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or	31/01/2011	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2010	n/a	PL	
IB/0037	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	06/12/2010	n/a		
IB/0036/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	07/10/2010	n/a		

	material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
II/0035	Changes relating to the active substance including: - Addition of an alternative manufacturer for an intermediate of the active substance; - Change to the manufacturing process of an	22/04/2010	04/05/2010		

	intermediate of the active substance; - Change the specifications of an intermediate of the active substance. Change(s) to the manufacturing process for the active substance				
IA/0034	IA_37_a_Change in the specification of the finished product - tightening of specification limits	20/11/2009	n/a		
II/0033	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	27/05/2009	SmPC and PL	The marketing authorisation holder identified 25 case reports (including 5 with severe hypoxemia) of interstitial lung disease in patients treated with Rilutek. Interstitial lung disease is associated with respiratory symptoms such as cough or difficulties in breathing. One case was reported in pivotal clinical trials which enrolled a total of 493 patients with amyotrophic lateral sclerosis. In the majority of the reported cases and based on the information available, no explanation other than an association with riluzole was found for the occurrence of interstitial lung disease. Symptoms resolved after drug discontinuation and symptomatic treatment in most cases. In one instance, the symptoms re-appeared upon re-administration of Rilutek.
IA/0032	IA_05_Change in the name and/or address of a manufacturer of the finished product	28/05/2008	n/a	Annex II and PL	
II/0030	Update of section 5.2 of Summary of Product Characteristics to reflect the results of a comparative pharrmacokinetic study in Japanese and Caucasian volunteers. Section 4.8 of the SPC is also amended	19/03/2008	22/04/2008	SmPC, Labelling and PL	The MAH conducted an open-label, randomized, repeated oral administration study to compare the pharmacokinetics of riluzole and its active metabolite in healthy Japanese and Caucasian adult male subjects. The results suggest that

	to add a statement related to the monitoring of the hepatic function. The Package Leaflet is reviewed to reflect the outcome of a user testing exercise. Update of Summary of Product Characteristics, Labelling and Package Leaflet				some Japanese patients may have a reduced exposure to riluzole, whilst the levels of exposure to the active metabolite N-hydroxyriluzole were similar. Another objective of the study was to assess the safety and tolerance of riluzole. No serious adverse events were observed in this study. However, the study data indicates that Asian patients may be more susceptible to liver function test abnormalities.
IA/0031	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	29/02/2008	n/a		
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/01/2007	n/a	PL	
R/0027	Renewal of the marketing authorisation.	01/06/2006	28/07/2006	SmPC, Annex II, Labelling and PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/03/2006	n/a	PL	
II/0025	Update of Summary of Product Characteristics, Labelling and Package Leaflet	17/11/2005	23/12/2005	SmPC, Annex II, Labelling and PL	The MAH applied for a variation to update section 4.4 and 4.8 of the SPC to include hepatitis as a very rare side effect. In addition section 4.9 has also been updated to more fully reflect the symptoms that have been seen following overdose of riluzole including neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma and methemoglobinemia, which have been observed in isolated cases. The proposed changes are in line with the available data from clinical trials, spontaneous reports and the published literature that has been submitted by the MAH. The PL was amended accordingly.

					With regard to hepatitis and hepatocellular injury, a search of the MAH's pharmacovigilance database (Clintrace) has identified several cases including cases from sponsored studies. Some of these cases were excluded due to insufficient information or non-serious event, or confounding by concomitant hepatatoxic medication, pre-existing and/or infectious liver disorder. Of the remaining cases, some described increases in liver enzymes that were in line with the currently approved SPC. The other cases described clinical hepatitis that occurred within 3 months of starting treatment. In four of these cases the patient fully recovered between 2 weeks and 3 months after riluzole treatment was stopped; in one of these cases the patient experienced a positive rechallenge. There was one fatal case. The available data would support the addition of hepatitis as a very rare side effect. The CHMP considered acceptable the wording in section 4.4 and 4.8 of the SPC proposed by the MAH. Concerning overdose, a total of 10 spontaneous reports of overdose of riluzole alone were received by the MAH, three of which were also published in the literature. Of these 10 cases, eight were considered to be serious. The most common symptom in these cases was methemoglobinemia; other symptoms were neurological and psychiatric symptoms, acute toxic encephalopathy with stupor and coma. The
IA/0026	IA_05_Change in the name and/or address of a manufacturer of the finished product	13/12/2005	n/a	Annex II and PL	
IA/0024	IA_04_Change in name and/or address of a manuf.	13/12/2004	n/a		

	of the active substance (no Ph. Eur. cert. avail.)				
II/0022	Quality changes	16/09/2004	21/09/2004		
IA/0023	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	29/07/2004	n/a		
IA/0021	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/05/2004	n/a	Annex II and PL	
II/0020	Quality changes Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC, Annex II, Labelling and PL	
II/0017	Update of Summary of Product Characteristics and Package Leaflet	22/08/2002	20/11/2002	SmPC and PL	
I/0018	15_Minor changes in manufacture of the medicinal product	29/10/2002	30/10/2002		
I/0014	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	12/02/2002	22/03/2002	Annex II and PL	
I/0013	20_Extension of shelf-life as foreseen at time of authorisation	11/12/2001	05/03/2002	SmPC	
I/0016	16_Change in the batch size of finished product	15/02/2002	27/02/2002		
I/0015	15_Minor changes in manufacture of the medicinal product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	21/02/2002	27/02/2002		

R/0012	Renewal of the marketing authorisation.	25/04/2001	11/07/2001	SmPC, Annex II, Labelling and PL	
I/0011	11a_Change in the name of a manufacturer of the active substance	15/09/2000	11/03/2001		
I/0010	01_Change in the name of a manufacturer of the medicinal product	15/09/2000	n/a	Annex II and PL	
I/0009	03_Change in the name and/or address of the marketing authorisation holder	15/09/2000	n/a	SmPC, Labelling and PL	
II/0005	Update of Summary of Product Characteristics	23/09/1999	31/01/2000	SmPC	
I/0008	13_Batch size of active substance	20/12/1999	n/a		
I/0007	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	20/12/1999	n/a		
I/0006	12_Minor change of manufacturing process of the active substance 12a_Change in specification of starting material/intermediate used in manuf. of the active substance	20/12/1999	n/a		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	25/02/1998	15/06/1998	SmPC and PL	

II/0003	Update of Summary of Product Characteristics	18/06/1997	08/10/1997	SmPC	
I/0002	25_Change in test procedures of the medicinal product	23/10/1996	n/a		
I/0001	24_Change in test procedure of active substance	23/10/1996	n/a		