Caprelsa

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
IA/0061	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/08/2023	n/a		
IAIN/0060/G	This was an application for a group of variations.	11/08/2023		Annex II and	

[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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union

	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure			PL	
IB/0057	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/07/2023	n/a		
IAIN/0058	A.1 - Administrative change - Change in the name and/or address of the MAH	11/07/2023		SmPC, Labelling and PL	
PSUSA/9327/ 202210	Periodic Safety Update EU Single assessment - vandetanib	12/05/2023	n/a		PRAC Recommendation - maintenance
PSUSA/9327/ 202204	Periodic Safety Update EU Single assessment - vandetanib	10/11/2022	12/01/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9327/202204.
II/0043	Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC to reflect the restriction of the indication for Caprelsa (vandetanib) for the treatment of aggressive and	15/09/2022	28/11/2022	SmPC, Annex II and PL	

	symptomatic RET mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease based on the results of the D4200C00104 study and the re-evaluation of efficacy in RET negative patients from study D4200C00058, both previously listed as a specific obligation in the Annex II; the Package Leaflet is updated accordingly. As a result of this variation, the SmPC, Annex II and PL are also updated to reflect the completion of the specific obligations and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligations. In addition, the Dutch translation of the Caprelsa (vandetanib) Product Information is rectified. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0055	Renewal of the marketing authorisation.	15/09/2022	15/11/2022		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0052	Update of sections 4.2 and 4.4 of the SmPC in order to amend an existing warning on renal failure based on safety signal evaluation report. In addition, the	22/04/2022	30/05/2022	SmPC and PL	Renal failure has been reported in patients treated with vandetanib. Dose interruptions, adjustments, or discontinuation may be necessary. Vandetanib exposure is

	MAH took the opportunity to update the contact details for local representative in DE in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				increased in patients with impaired renal function. Vandetanib starting dose should be reduced to 200 mg in patients with moderate renal impairment (creatinine clearance ≥30 to <50 mL/min) and the QT interval should be closely monitored. Vandetanib is not recommended for use in patients with severe renal impairment (clearance below 30 mL/min). There is no information available for patients with end-stage renal disease requiring dialysis. For more information, please refer to the Summary of Product Characteristics.
R/0050	Renewal of the marketing authorisation.	11/11/2021	11/01/2022		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/9327/ 202104	Periodic Safety Update EU Single assessment - vandetanib	11/11/2021	11/01/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9327/202104.
IAIN/0053/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	02/12/2021	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place 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				
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2021	11/01/2022	PL	
IA/0048/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	04/06/2021	11/01/2022	Annex II and PL	
R/0046	Renewal of the marketing authorisation.	15/10/2020	09/12/2020		
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/11/2020	11/01/2022	PL	
PSUSA/9327/ 202004	Periodic Safety Update EU Single assessment - vandetanib	29/10/2020	n/a		PRAC Recommendation - maintenance
II/0044/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a	01/10/2020	n/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 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
R/0041	Renewal of the marketing authorisation.	14/11/2019	13/01/2020		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the

					opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/9327/ 201904	Periodic Safety Update EU Single assessment - vandetanib	31/10/2019	n/a		PRAC Recommendation - maintenance
IAIN/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/10/2019	13/01/2020	SmPC and PL	
II/0040	Submission of an updated RMP version 13 in order to remove the Health Care Professionals survey from the list of additional Pharmacovigilance Activities and to remove several safety concerns from the list of important identified and potential risks and missing information to follow revised guidance in the GVP Module V Rev.2 as requested during variation procedure EMEA/H/C/002315/II/0028. 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	03/10/2019	n/a		
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/06/2019	13/01/2020	PL	

II/0028	Update of Annex II to modify the specific obligation SOB 001 to ensure that comprehensive data are generated by the agreed due date. The revised RMP version 12.4 is acceptable. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10 and to update the list of local representatives in Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/02/2019	13/01/2020	SmPC, Annex II and PL	The Annex II has been updated as follows: In order to confirm the efficacy and safety of Caprelsa in RET-negative patients, the MAH should submit: - the clinical study report of study D4200C00104, an observational study including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic thyroid cancer (MTC). - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study D4200C00058. Due date: 3Q 2020
IA/0036	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	26/02/2019	n/a		
IA/0037/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	12/02/2019	n/a		

R/0032	Renewal of the marketing authorisation.	15/11/2018	15/01/2019		
IG/1003	A.1 - Administrative change - Change in the name and/or address of the MAH	20/12/2018	13/01/2020	SmPC, Labelling and PL	
IA/0034/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/11/2018	n/a		
PSUSA/9327/ 201804	Periodic Safety Update EU Single assessment - vandetanib	31/10/2018	n/a		PRAC Recommendation - maintenance
IAIN/0033/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	16/10/2018	15/01/2019	Annex II and PL	
II/0029	Update of section 5.3 of the SmPC to reflect the results from pre-clinical study titled "ZD6474: A 104	31/05/2018	15/01/2019	SmPC	Vandetanib has shown no carcinogenic potential effect in a 6 month carcinogenicity study in rasH2 transgenic mice. A

	Week Carcinogenicity Study by Oral Gavage in Rats", study number 521826. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				2-year carcinogenicity study in rats was impaired by low survival in the high dose female group and limited exposure of the animals to vandetanib; however, no carcinogenic effects were observed in the remaining animals.
II/0030	Update of section 5.1 of the SmPC to add information on overall survival based on the addendum to clinical study report from the study D4200C00058 (cut-off date 2015): An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer. In addition, the Marketing authorisation holder took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	15/01/2019	SmPC and PL	Survival status and the median final overall survival (81.6 months in the vandetanib arm and 80.4 months in the placebo arm) were similar across both treatment arms. There was no statistically significant difference in final OS (HR 0.99, 95.002% CI 0.72, 1.38, p=0.9750). Results should be interpreted with caution due to the high percentage of patients in the placebo arm switching to open-label vandetanib (79.0% [79/100] of patients).
R/0027	Renewal of the marketing authorisation.	14/12/2017	09/02/2018		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II

					to the opinion.
PSUSA/9327/ 201704	Periodic Safety Update EU Single assessment - vandetanib	26/10/2017	n/a		PRAC Recommendation - maintenance
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2017	09/02/2018	PL	
R/0023	Renewal of the marketing authorisation.	15/12/2016	17/02/2017		
II/0016	Extension of Indication to include paediatric patients aged 5 to 18 with unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC) for Caprelsa; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information from studies IRUSZACT0098, ISSZACT0004, IRUSZACT0051 and IRUSZACT0061. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	10/11/2016	16/12/2016	SmPC, Annex II, Labelling and PL	Please refer to the published Assessment Report Caprelsa H-2315-II-16-AR
IAIN/0024/G	This was an application for a group of variations. 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	14/12/2016	17/02/2017	Annex II and PL	

	manufacturing site for the FP - Primary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
PSUSA/9327/ 201604	Periodic Safety Update EU Single assessment - vandetanib	27/10/2016	n/a		PRAC Recommendation - maintenance
T/0022	Transfer of marketing authorisation from AstraZeneca AB. to Genzyme Europe B.V. Transfer of Marketing Authorisation	15/08/2016	08/09/2016	SmPC, Labelling and PL	
II/0013	Submission of the Clinical Study Report for Part A of Study D4200C00097, undertaken to evaluate the safety and efficacy of vandetanib 150 and 300 mg/day in patients with unresectable locally advanced or metastatic medullary thyroid carcinoma with progressive or symptomatic disease, in order to address the post-authorisation measure MEA 002. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/06/2016	n/a		N/A
IB/0019	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/04/2016	08/09/2016	SmPC, Annex II and PL	

IA/0020	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	13/04/2016	n/a		
PSUSA/9327/ 201504	Periodic Safety Update EU Single assessment - vandetanib	19/11/2015	14/01/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9327/201504.
R/0015	Renewal of the marketing authorisation.	22/10/2015	16/12/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IG/0633	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	09/12/2015	n/a		
PSUSA/9327/ 201410	Periodic Safety Update EU Single assessment - vandetanib	10/04/2015	n/a		PRAC Recommendation - maintenance
R/0009	Renewal of the marketing authorisation.	23/10/2014	15/01/2015		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the

					opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
PSUV/0010	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
II/0011	Update of section 5.3 of the SmPC in order to incorporate the results of a 6-month mouse carcinogenicity study. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	15/01/2015	SmPC	
IB/0008	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	02/06/2014	n/a		
PSUV/0006	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IG/0402	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	27/02/2014	n/a		
R/0005	Renewal of the marketing authorisation.	24/10/2013	20/12/2013	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and

					sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
II/0004/G	This was an application for a group of variations. Update of section 4.5 of the SmPC further to the results of drug-drug interaction studies with digoxin, metformin, antacids (omeprazole or ranitidine) and midazolam, conducted to fulfil additional pharmacovigilance activities (MEA 005, 006, 007 and 008). 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	18/12/2013	15/01/2015	SmPC	Four drug-drug interactions between vandetanib and digoxin, omeprazole/ranitidine, metformin and midazolam were evaluated as post-authorisation measures for the marketing authorisation of Caprelsa (vandetanib). The results of these drug-drug interaction studies described adequately in section 4.5 of the Summary of Product Characteristics (SmPC).
R/0002	Renewal of the marketing authorisation.	13/12/2012	18/02/2013	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and

					sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Caprelsa, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IB/0003	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	13/12/2012	n/a		
IAIN/0001/G	This was an application for a group of variations. C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	22/06/2012	n/a		