Oncaspar

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
IB/0055	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/10/2024	n/a		
II/0053/G	This was an application for a group of variations.	16/05/2024		SmPC and PL	SmPC new text: Hepatic veno-occlusive disease (VOD) , including severe,

[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).

	- Type II (C.I.4): Update of sections 4.4 and 4.8 of the SmPC in order to add 'Hepatic veno-occlusive disease (VOD)' as a warning and new safety risk with 'not known' frequency, following an internal signal evaluation. The Package Leaflet is updated accordingly. - Type IB (C.I.3.z): Update of sections 4.4 and 4.8 of the SmPC in order to add 'Antithrombin III decreased' to the list of adverse drug reactions with frequency 'Very common' and to update the frequency of 'Neutrophil count decreased' from 'Not known' to 'Very common', following the outcome of the PAM procedure P46/008. The Package Leaflet is updated accordingly. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				life-threatening and potentially fatal cases have been observed in patients treated with Oncaspar in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy (see section 4.8). Signs and symptoms of VOD include rapid weight gain, fluid retention with ascites, hepatomegaly, thrombocytopenia and rapid increase of bilirubin. The identification of risk factors like pre-existing liver disease or history of VOD is essential for its prevention. Prompt recognition and appropriate management of VOD remain imperative. Patients who experience this condition should be treated according to standard medical practice. For more information, please refer to the Summary of Product Characteristics.
IB/0052/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.1.k - Change in the manufacturer of AS or of a	22/06/2023	n/a		

	starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB				
PSUSA/10457 /202207	Periodic Safety Update EU Single assessment - pegaspargase (centrally authorised product)	16/03/2023	n/a		PRAC Recommendation - maintenance
IB/0051	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/01/2023	11/01/2024	Annex II	
II/0048	Update of sections 4.2 and 4.4 of the SmPC in order to add advice on premedication to reduce the cases of hypersensitivity reactions based on literature review and guidelines. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2022	13/09/2022	SmPC and PL	In order to decrease the risk and severity of infusion and hypersensitivity reactions, patients should be premedicated with paracetamol, an H-1 receptor blocker, and an H-2 receptor 30-60 minutes prior to administration of Oncaspar patients should be premedicated with paracetamol, an H-1 receptor blocker, and an H-2 receptor blocker. For more information, please refer to the Summary of Product Characteristics.
IB/0049/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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	08/09/2022	n/a		

IB/0047	C.I.7.a - Deletion of - a pharmaceutical form	02/06/2022	24/06/2022	SmPC, Labelling and PL	
II/0045/G	This was an application for a group of variations. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS A.7 - Administrative change - Deletion of manufacturing sites 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)	05/05/2022	n/a		
IB/0046/G	This was an application for a group of variations. 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.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	25/04/2022	n/a		

	batch control/testing takes place				
II/0038	Update of sections 4.4, 4.5 and 4.8, of the SmPC in order to add a new warning on the risk of osteonecrosis and to include it as an adverse drug reaction associated with pegaspargase use with an unknown frequency, following review of all available non-clinical, epidemiological and clinical data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	24/06/2022	SmPC and PL	Pegaspargase may increase the risk of glucocorticoid-induced osteonecrosis in children and adolescents with a higher incidence seen in girls. Therefore, when pegaspargase is co-administered with glucorticoids a close monitoring in children and adolescents' patients is recommended in order to detect any clinical signs/symptoms of osteonecrosis. For more information, please refer to the Summary of Product Characteristics.
IB/0044	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/12/2021	n/a		
IB/0042	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	01/10/2021	n/a		
IB/0043	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	01/09/2021	n/a		
IB/0041/G	This was an application for a group of variations.	29/07/2021	n/a		

	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.b - Change in the specification parameters and/or limits of an AS, starting 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters				

	and/or limits of the finished product - Tightening of specification limits				
IAIN/0040/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/05/2021	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.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	22/03/2021	n/a		
II/0036/G	This was an application for a group of variations. Group of 2 Type II variations to submit (1) the final study results of Study 12-266 A(12), an open label single arm phase II trial evaluating the efficacy and toxicity of treatment regimens including Oncaspar in adults (aged 18-60) with newly diagnosed Philadelphia chromosome-negative acute	11/02/2021	24/06/2022	SmPC and Annex II	The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II: - Study 12-266 A(12): "Post-authorisation efficacy study (PAES): In order to further define the efficacy and safety of Oncaspar in adult patients with acute lymphoblastic leukaemia, the MAH should submit the results of a multicentre, open label single arm phase II trial evaluating the efficacy and toxicity of treatment regimens

	lymphoblastic leukaemia and (2) interim results of Study CAALL-F01, a prospective multicentre cohort study evaluating Oncaspar used in the first-line treatment of children and adolescents with ALL along with multi-agent chemotherapy. Consequently, Annex II updated to remove Study 12-266 A(12). The RMP (version 4.1) is updated accordingly. An editorial change has been added to the SmPC. 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 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				including Oncaspar in adults (aged 18-60) with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukaemia.”
IB/0037/G	This was an application for a group of variations. 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.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	25/11/2020	n/a		

R/0034	Renewal of the marketing authorisation.	17/09/2020	20/11/2020	SmPC and PL	
II/0035	B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs	03/09/2020	n/a		
IB/0032/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.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.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	02/07/2020	n/a		

PSUSA/10457 /201907	Periodic Safety Update EU Single assessment - pegaspargase (centrally authorised product)	27/02/2020	23/04/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10457/201907.
IA/0033/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	17/04/2020	n/a		
IA/0031/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.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	17/03/2020	n/a		
IB/0030	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)	12/02/2020	23/04/2020	SmPC and PL	

IA/0028/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.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.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.d - Change in the specification parameters and/or limits of an AS, starting	25/09/2019	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IA/0027/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/09/2019	n/a		
IB/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/07/2019	09/03/2020	Annex II	
PSUSA/10457 /201807	Periodic Safety Update EU Single assessment - pegaspargase (centrally authorised product)	28/02/2019	26/04/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10457/201807.
IAIN/0025	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	29/03/2019	09/03/2020	Annex II and PL	
IB/0024	C.I.11.z - Introduction of, or change(s) to, the	25/03/2019	09/03/2020	Annex II	

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
T/0021	Transfer of Marketing Authorisation	19/10/2018	10/12/2018	SmPC, Labelling and PL	
IAIN/0023	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	06/12/2018	26/04/2019	Annex II and PL	
II/0016/G	This was an application for a group of variations. Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC based on the final results from studies DFCI 11-001 and AALL07P4 listed as category 3 studies in the Risk Management Plan: Study DFCI 11-001 is a Phase 2, open-label, randomized, multicenter study to determine the safety and feasibility of administering an investigational asparaginase product (asparaginase formulation) compared with Oncaspar in subjects aged 1 to <22 years with newly diagnosed Acute Lymphoblastic Leukaemia (ALL) and lymphoblastic lymphoma. Study AALL07P4 is a multicenter, open label, randomized, active-controlled, parallel design clinical pilot study conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity and efficacy of an investigational	04/10/2018	10/12/2018	SmPC and PL	The pharmacodynamic effect of Oncaspar was assessed after IM (Study CCG 1962) and IV administration (AALL07P4). Based on results from these two studies, a 2,500 U/m2 BSA dose of Oncaspar administered IM (CCG 1962) and IV (AALL07P4) provides maintenance of L asparagine depletion for approximately two weeks following dosing. The results on pharmacokinetic properties were reflected in section 5.2. Overall, results indicate that, when Oncaspar 2,500 U/m2 BSA is administered as single and repeated doses every two weeks, clinically relevant asparaginase activity is sustained over the entire dosing interval (i.e. two weeks). Results from Study CCG-1962 from the initial application were also reflected. The controlled studies were not designed to formally evaluate the pharmacokinetics of Oncaspar in specific populations. A population pharmacokinetic evaluation of Oncaspar based on data obtained from Studies AALL07P4 (IV), DFCI 11 001 (IV), and CCG 1962 (IM) identified that clearance (linear and saturable) increased approximately proportional to BSA

	asparaginase product in comparison with Oncaspar in patients aged 1 to <31 years newly diagnosed with high risk B-precursor ALL. The Package Leaflet has been updated accordingly. 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				and volume of distribution increased slightly more proportional to BSA. No statistically significant differences in PK characteristics between male and female subjects were identified in this analysis. The impact of renal and hepatic impairment on the PK of Oncaspar has not been evaluated. The existing warning concerning hepatitis and pancreatitis was reworded, and monitoring of serum amylase and/or lipase levels was added to be monitored frequently to identify early signs of pancreatic inflammation. As impaired glucose tolerance may occur with concomitant use of Oncaspar with prednisone, blood glucose levels should be monitored. The existing contraindication in patients with history of pancreatitis has been updated to include pancreatitis related to previous L asparaginase therapy. New adverse reactions have been reported from these studies, namely increase of aspartate aminotransferase and lipase levels, embolism, ascites, hypoalbuminaemia, hypokalaemia, increase of international normalized ratio. Hypersensitivity reactions including angioedema, lip swelling, eye swelling, erythema, decreased blood pressure, bronchospasm, dyspnoea and pruritus were observed in these studies and further described in the SmPC . Warning was reworded in order to specify that patients with known hypersensitivity to E. coli derived asparaginase formulations should be aware of possible hypersensitivity reactions, whereas Philadelphia chromosome positive patients for whom treatment with tyrosine kinase inhibitors (e.g. imatinib) is combined with L asparaginase may be at increased risk for hepatotoxicity. Combination therapy with Oncaspar and hepatotoxic

					products can result in severe hepatic toxicity and those patients should be monitored for changes in liver function parameters. Due to the risk of hyperbilirubinaemia, it is recommended to monitor bilirubin levels at baseline and prior to each dose, whereas ammonia levels should be monitored closely in case of hyperammonaemia symptoms (nausea, vomiting, headache, dizziness and rash). Warning was reviewed to clearly indicate that Oncaspar may also cause myelosuppression and therefore increase the risk of infections. It is strongly recommended that every time Oncaspar is administered to a patient, the name and lot number of the product are recorded in order to link the patient and the lot of the product and thereby closely monitor patients for any adverse reactions throughout the administration period.
IA/0019/G	This was an application for a group of variations. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	27/07/2018	n/a		
PSUSA/10457 /201801	Periodic Safety Update EU Single assessment - pegaspargase (centrally authorised product)	12/07/2018	n/a		PRAC Recommendation - maintenance
IA/0018	B.I.b.1.d - Change in the specification parameters	02/05/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IB/0014/G	This was an application for a group of variations. B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.e - Stability of FP - Change to an approved stability protocol	27/03/2018	10/12/2018	SmPC, Labelling and PL	
IB/0015	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	15/03/2018	n/a		
PSUSA/10457 /201707	Periodic Safety Update EU Single assessment - pegaspargase (centrally authorised product)	08/02/2018	n/a		PRAC Recommendation - maintenance
X/0008	Annex I_2.(d) Change or addition of a new pharmaceutical form	12/10/2017	08/12/2017	SmPC, Annex II, Labelling and PL	
IB/0013/G	This was an application for a group of variations. B.II.b.z - Change in manufacture of the Finished Product - Other variation B.II.f.z - Stability of FP - Other variation	30/11/2017	n/a		
PSUSA/10457	Periodic Safety Update EU Single assessment -	01/09/2017	n/a		PRAC Recommendation - maintenance

/201701	pegaspargase (centrally authorised product)				
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2017	08/12/2017	Labelling and PL	
IAIN/0010	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	12/05/2017	08/12/2017	SmPC, Annex II, Labelling and PL	
IA/0007/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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	10/02/2017	n/a		
PSUSA/10457 /201607	Periodic Safety Update EU Single assessment - pegaspargase (centrally authorised product)	09/02/2017	n/a		PRAC Recommendation - maintenance
IB/0006	B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	02/02/2017	n/a		
IA/0003	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	22/06/2016	n/a		

	variation				
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/04/2016	08/12/2017	PL	
IB/0001	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	07/03/2016	n/a		