Javlor

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/0025/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/04/2024		SmPC, Annex II and PL	

[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/0024	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/11/2022	n/a		
PSUSA/3123/ 202109	Periodic Safety Update EU Single assessment - vinflunine	05/05/2022	n/a		PRAC Recommendation - maintenance
IAIN/0023/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	02/02/2022	23/05/2023	SmPC, Annex II, Labelling and PL	
IAIN/0021	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	07/01/2021	24/01/2022	Annex II and PL	
PSUSA/3123/ 201809	Periodic Safety Update EU Single assessment - vinflunine	16/05/2019	n/a		PRAC Recommendation - maintenance
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2018	24/01/2022	Labelling	
PSUSA/3123/ 201609	Periodic Safety Update EU Single assessment - vinflunine	06/04/2017	n/a		PRAC Recommendation - maintenance
PSUSA/3123/ 201509	Periodic Safety Update EU Single assessment - vinflunine	14/04/2016	n/a		PRAC Recommendation - maintenance

PSUSA/3123/ 201409	Periodic Safety Update EU Single assessment - vinflunine	10/04/2015	n/a		PRAC Recommendation - maintenance
PSUV/0015	Periodic Safety Update	25/04/2014	19/06/2014	SmPC and PL	The MAH proposed to add a warning to section 4.4 of the SmPC regarding the risk of hyponatraemia, including cases that are due to syndrome of inappropriate antidiuretic hormone secretion, which was identified as a risk in the previous PSUR and included in the SmPC as a listed adverse reaction. Given the high frequency of grade 3 or 4 events of hyponatraemia (11.7 %), which includes a fatal outcome, the adverse impact of hyponatraemia on survival in cancer patients and the potential for it to cause serious CNS sequelae (e.g. confusion, seizures), this proposal was endorsed. The MAH also proposed minor amendments to the list of adverse reactions in section 4.8 of the SmPC in order to ensure consistency in how these reactions are coded. The changes do not impact on the frequency categories for the listed ADRs apart from "peripheral sensory neuropathy" which is upgraded from common to very common and "tumour pain", which is now categorised as uncommon (previously its frequency was not known). No new ADRs have been added and no ADRs have been removed, other than "anorexia" which has been re-classified as "decreased appetite". Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation.
R/0014	Renewal of the marketing authorisation.	20/03/2014	16/05/2014	SmPC, Annex II, Labelling	

				and PL	
IB/0013/G	This was an application for a group of variations. 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.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.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	14/01/2014	n/a		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2013	16/05/2014	PL	
IAIN/0010	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/02/2013	n/a		
II/0007/G	This was an application for a group of variations. This was an application for a group of variations.	24/05/2012	27/06/2012	SmPC, Annex II, Labelling	The MAH identified a total of four cases of PRES following vinflunine use over the period December 1998 to May 2011. These included one clinical trial and three post-

	Update of sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) to include information on "Posterior Reversible Encephalopathy Sydrome" (PRES) and "Tumor Pain" as adverse reactions. Section 2 of the Package Leaflet (PL) has been updated accordingly. Further editorial changes were made to sections 4.2 and 4.6 of the SmPC, and the Package Leaflet. In addition, the MAH also took the opportunity to include minor editorial changes to adapt the Product Information to the new QRD template (v8.1). 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 MAH C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH			and PL	marketing reports. Therefore, as a risk minimisation measure, the MAH included a recommendation for blood pressure control and reference to brain imaging to confirm a diagnosis of PRES in section 4.4 of the SmPC. The frequency for PRES ('rare') was calculated based on a non-TCCU clinical trial report and was included in section 4.8 of the SmPC. A total of three cases of tumour pain following Javlor use were also reported post marketing. An association of the adverse reaction with the drug was plausible in these cases. The frequency of this adverse reaction could not be estimated from post-marketing data, hence "frequency not known" was included in section 4.8 of the SmPC.
IB/0008	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	26/06/2012	29/10/2012	SmPC	

IAIN/0009/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	12/06/2012	n/a		
II/0006	Update of sections 4.2 "Posology and Method of Administration" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics (SmPC) in order to include the results and conclusions of Study L00070 IN 113, as requested in FUM 2. 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 MAH	22/09/2011	10/11/2011	SmPC	Following the assessment of FUM2, the MAH has updated the following sections of the SmPC; section 4.2 to note that in renally impaired patients, further cycles should be adjusted in the event of toxicities, and that the recommended dose after Cycle 1 in such cases should be the same as that specified for elderly patients; section 5.2 to provide a brief descriptive update regarding study L00070 IN 113, concluding that Vinflunine clearance is reduced when creatinine clearance is decreased.
II/0004/G	This was an application for a group of variations. Update of sections 4.2, 4.3, 4.4, 4.5 and 4.8 of the Summary of Product Characteristics (SmPC) following the assessment of PSUR 1. The Marketing Authorisation Holder (MAH) has also taken the opportunity to update sections 4.6, 4.7, 5.1, 6.2 and 10 of the SmPC and Annex II B with	22/09/2011	10/11/2011	SmPC, Annex II and PL	Following the assessment of PSUR1, the MAH has updated the following sections of the SmPC; section 4.2 to provide further information on adequate monitoring of platelets and haemoglobin, dose delays or discontinuation due to toxicity in patients with neutropenia, thrombocytopenia, organ toxicity or cardiac ischaemia, additional precision in the grading of toxicities such as mucositis, constipation, nausea, and vomiting, and recommendations on dose

	minor editorial changes. Sections 2, 3 and 4 of the Package leaflet have been updated accordingly. 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 MAH 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 MAH C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				adjustments for patients with hepatic impairment and the elderly; section 4.3 to clarify the contraindications with regards to neutrophil and platelet count; section 4.4 to include leucopenia, anaemia and thrombocytopenia as adverse reactions, a cross reference to section 4.3 with regards to the contraindication on baseline neutrophil and platelet count, deletion of "cumulative constipation", replacement of "heavy abdominal surgery" by "major abdominal surgery", replacement of "polyethylene glycol" with "an osmotic laxative", additional precisions on the use of laxatives and further information on the grading of gastrointestinal toxicity; section 4.5 with further information on the potential for interaction between vinflunine and doxorubicin; section 4.8 to add rash, urticaria and erythema and skin and subcutaneous tissue disorders. Sections 4.6, 4.7, 5.1, 6.2,10 of the SmPC and Annex II B have been updated with minor editorial comments and section 2, 3 and 4 of the Package Leaflet (PL) have been aligned with the SmPC.
IA/0005/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV 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)	23/06/2011	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0002	Update of section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SmPC) to amend the frequencies of adverse events, which are inaccurate. The Marketing Authorisation Holder (MAH) has also taken the opportunity to update Section 4.2, 4.4, 4.5, 4.6, 5.2, 5.3, 6.2, 6.3 and 6.6 of the SmPC with minor editorial/linguistic changes, and the relevant section in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC and PL	The MAH has amended the frequencies of adverse events in section 4.8 "Undesirable effects" of the SmPC, arguing that the methodology initially used to calculate the worst grade by patient of each grouping term was incorrect. This calculation was inaccurate due to the fact that the patients who experienced several individual MedDRA preferred terms of the same group were counted several times within this group. The adverse events affected by these changes are infections (viral, bacterial, fungal), visual disturbances, sensory peripheral neuropathy, common cough, dyspnoea, abdominal pain, constipation, ileus, buccal disorders, cutaneous reactions, pruritus, arthralgia, ashtenia/fatigue, injection site reactions, chest pain, transaminase increase, neutropenia, severe anaemia, thrombocytopenia, and febrile neutropenia. At the same time, the MAH has made minor editorial/linguistic changes to Section 4.2, 4.4, 4.5, 4.6, 5.2, 5.3, 6.2, 6.3 and 6.6 of the SmPC and the PL.
II/0001	Update of sections 4.2, 4.4 and 5.2 of the Summary of Product Characteristics (SmPC) with dose adjustments for the elderly population following the submission of the final study report of L00070IN 114 "Pharmacokinetic Study of IV Vinflunine in Elderly Cancer Patients" to fullfull FUM 003. The Marketing Authorisation Holder (MAH) has also taken the opportunity to update Section 3 of the Package leaflet accordingly. Annex II B has been updated in line with the EC	18/11/2010	20/12/2010	SmPC, Annex II and PL	Further to the request of the CHMP to fulfill FUM 003, the MAH has included dose adjustments in sections 4.2 "Posology and Method of Administration, 4.4 "Special Warnings and Precautions for Use", and 5.2 Pharmacokinetic Properties of the SmPC, in elderly patients aged 75 years or more. The MAH has also updated section 3 of the PL to align it with the SmPC, reflecting the need to adjust the dose of vinflunine based on the age, physical conditions, and specific situation of the patient.

	decision to delete the version number of the DDPS. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IB/0003	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	30/07/2010	n/a		