EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Kepivance

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/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/03/2016	22/03/2016	SmPC and PL	
PSUSA/2265/ 201501	Periodic Safety Update EU Single assessment - PALIFERMIN	10/09/2015	n/a		PRAC Recommendation - maintenance
IB/0043	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	02/10/2014	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).

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IAIN/0042	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	08/04/2014	n/a		
IA/0041	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	04/07/2013	n/a		
IB/0040/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.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.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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/06/2013	n/a		

II/0039/G	This was an application for a group of variations. Update of section 4.5 of the SmPC with information on the interaction of heparin and palifermin. Update of sections 4.2 and 5.1 and 5.2 of the SmPC further to results from a pharmacokinetic study in paediatric patients. Update of sections 4.2 and 5.2 of the SmPC with results from a pharmacokinetic study in elderly patients. The Package Leaflet was proposed to be updated accordingly. Annex II is also updated in line with the latest QRD template (version 9). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	03/06/2014	SmPC, Annex II and PL	Interaction with heparin In-vitro and in-vivo data suggests that palifermin binds to unfractionated as well as low molecular weight heparins. In two studies in healthy volunteers, co-administration of Kepivance and heparin resulted in approximately 5 times higher systemic exposure to palifermin, due to a lower volume of distribution. The pharmacodynamic effect of palifermin, as measured by the change in Ki67 expression, tended to be lower when administered with heparin but the clinical relevance of this finding is unclear. However, the administration of palifermin did not affect heparin´s anticoagulant effect in the experimental conditions (single dose, subtherapeutic dose regimen). Due to limited data in patients, heparins should be used with care in patients receiving palifermin and appropriate blood coagulation tests should be carried out to monitor their treatment. Paediatric population The safety and efficacy of Kepivance in children aged 0 to 18 years have not been established. A phase I dose escalation study was conducted in paediatric patients aged 1-16 years. A total of 27 paediatric patients with leukaemia were randomized to 40, 60 or 80 micrograms/kg/day of palifermin for 3 days pre- and post-hematopoietic stem cell transplantation (HSCT). The conditioning regimen consisted of total body irradiation (TBI), etoposide and cyclophosphamide. There was a lower incidence of severe oral mucositis in patients receiving 80 micrograms/kg/day but no effect on the incidence of acute graft-versus-host disease (GVHD). Although palifermin was safe at all doses tested the incidence of skin reactions increased with the dose. In a small multiple-dose study in paediatric patients (1 to

					16 years old) receiving 40, 60 or 80 micrograms/kg/day for 3 days pre- and post- HSCT, there was no effect of age on the pharmacokinetics of palifermin although a large variability was observed in the estimated parameters. Systemic exposure did not appear to increase with the dose. Based on the available data, no recommendation on a posology in paediatric patients can be made. Older people Safety and efficacy has not been evaluated in older people. In a single dose study the clearance of palifermin was approximately 30% lower in 8 healthy subjects aged 66-73 years after a dose of 90 micrograms/kg than in younger subjects (≤ 65 years) after a dose of 180 micrograms/kg. Based on these limited data no recommendation on dose adjustment can be made.
IB/0038	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	22/11/2012	n/a		
IB/0037/G	This was an application for a group of variations. B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) A.7 - Administrative change - Deletion of manufacturing sites B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	27/09/2012	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation				
IB/0036	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	01/08/2012	n/a		
IB/0035	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	09/07/2012	25/10/2012	SmPC	
IG/0162	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	30/03/2012	n/a		
IB/0033	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	29/02/2012	n/a		
IB/0031	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	18/01/2012	n/a		
IB/0032	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	09/12/2011	n/a		
II/0029	Update of sections 4.4 and 5.1 of the Summary of Product Characteristics (SmPC) with regard to the	17/03/2011	02/05/2011	SmPC and PL	At the time of the granting of the initial marketing authorisation, the Marketing Authorisation Holder (MAH)

	cataractogenic effect of palifermin further to clinical study results, as requested by the CHMP in the assessment of FUM 026. The MAH also proposed to update the package leaflet further to the results of consultation with target patient group. 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				committed to conduct clinical study to determine the incidence and risk of cataracts and decreased visual acuity. Results of this study showed that cataractogenic effects of palifermin cannot be excluded following results of ophthalmologic examinations in a subset of patients (n=66; 14 in the placebo group, 52 in the palifermin group) who were followed for 12 months after the acute phase of the above post-approval study. For the primary endpoint, which was incidence of cataract development or progression at 12 months (defined as an increase of ? 0.3 in the LOCS III score), a greater proportion of subjects experienced cataract development in the palifermin group compared with the placebo group (28.6 % in the placebo group vs 48.1% in the palifermin group). This difference was not statistically significant. Visual acuity was not affected at 6 or 12 months in either treatment group. There was an imbalance in age distribution with more elderly (>65 years) patients in the palifermin group.
IA/0030/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.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance	02/02/2011	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0028/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 responsible for batch release 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	02/12/2010	n/a	SmPC, Annex II, Labelling and PL	
R/0027	Renewal of the marketing authorisation.	22/07/2010	23/09/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Kepivance continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. However, due to recent additional risks in the risk management plan and restriction of indication, the CHMP considers that the MAH should continue to submit yearly PSURs.
II/0024	Update of section 4.1 of the Summary of Product	18/03/2010	29/04/2010	SmPC and PL	At the time of the granting of the initial marketing

	Characteristics (SmPC) to restrict the indication to patients with haematological malignancies receiving myeloablative radiochemotherapy associated with a high incidence of severe mucositis and requiring autologous haematopoietic stem cell support, further to the results of Study 20050219 conducted as a follow-up measure (FU2 018.2). Consequently, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC have also been updated. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				authorisation, the Marketing Authorisation Holder (MAH) made a commitment to address the CHMP concerns regarding superiority of the pre-/post- dose compared with pre-only and regarding extrapolation of data from pivotal trial of total body irradiation (TBI)/chemotherapy-based regimens to chemotherapy-only based regimens. Study 20050219 was conducted by the MAH to address these concerns. It was a double-blind, randomised, placebo-controlled study of two different schedules of palifermin (pre chemotherapy only and pre plus post chemotherapy) for reduction of mucositis in subjects with multiple myeloma (MM) receiving high dose melphalan followed by autologous peripheral blood stem cell transplantation (PBSCT). In this variation application, the MAH submitted the final clinical study report 20050219 in order to fulfil this commitment (FU2 018.2). The primary objective of this study was to compare the efficacy of Palifermin relative to placebo when given either pre-high dose chemotherapy only or pre- and post-high dose chemotherapy by determining the incidence of oral mucositis (WHO grades 2, 3 and 4). The study included three treatment arms and was designed to compare each of the palifermin arms (pre- and pre/post-) to placebo. In this study (n=281), patients with multiple myeloma received conditioning with melphalan (200 mg/m2) prior to autologous haematopoietic stem cell transplantation.

					The incidence of ulcerative oral mucositis was 57.9% in the placebo arm, 68.7% in the pre/post CT group and 51.4% in the pre-CT group. Neither of the two dosing regimens demonstrated statistically significant results versus placebo. The incidence of severe (grades 3 and 4) oral mucositis in the 3 groups was 36.8%, 38.3% and 23.9% for the placebo, pre/post CT and pre-CT groups respectively, with no statistical significance being demonstrated. Treatment-emergent adverse events with respect to infections were reported
IA/0026	C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation	07/04/2010	n/a	Annex II	
IB/0025	To increase the shelf life of the active substance 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	24/02/2010	n/a		
IB/0023	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	15/12/2009	n/a	SmPC and PL	
IA/0022	IA_05_Change in the name and/or address of a manufacturer of the finished product	06/11/2009	n/a		
IA/0021	IA_09_Deletion of manufacturing site	08/10/2009	n/a		
IA/0020	IA_09_Deletion of manufacturing site	08/10/2009	n/a		
IA/0019	IA_09_Deletion of manufacturing site	08/10/2009	n/a		

IA/0018	IA_09_Deletion of manufacturing site	08/10/2009	n/a		
IA/0017	IA_09_Deletion of manufacturing site	06/10/2009	n/a		
II/0015	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	31/07/2009	SmPC and PL	This type II variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of FU2 042.1 and PSU 035(PSUR 6), with the ADRs 'vaginal oedema and erythema' and 'palmar-plantar erythrodysaestesia syndrome (dysaesthesia, erythema, oedema on the palms and soles) '. The Package Leaflet has been updated accordingly.
II/0012	Provision of DDPS (Pharmacovigilance) Changes to QPPV Update of DDPS (Pharmacovigilance)	29/05/2009	29/06/2009	Annex II	This type II variation concerns the provision of a Detailed Description of the Pharmacovigilance System (DDPS) in Module 1.8.1 (version 1.0). Consequently, Annex II has been updated with standard text to reflect the latest versions of the DDPS (version 1.0) and RMP (version 1.4) agreed with the CHMP.
IA/0016	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	04/06/2009	n/a	Annex II and PL	
IA/0014	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	14/04/2009	n/a		
IA/0013	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	10/02/2009	n/a		
T/0011	Transfer of Marketing Authorisation	05/11/2008	20/11/2008	SmPC, Labelling and PL	Transfer of the Marketing Authorisation from Amgen Europe B.V. to Biovitrum AB (publ).
II/0009	Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	07/07/2008	SmPC and PL	This type II variation concerns an update of section 4.5 of the SPC, upon request by CHMP following the assessment

					of FUM 024, with further information regarding potential interaction with heparin. In-vitro and in-vivo data suggests that palifermin binds to unfractionated as well as low molecular weight heparins, which should be used with care in patients who are concomitantly administered palifermin. The clinical relevance is unclear. Further, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.
II/0008	The Marketing Authorisation Holder applied for a revision of the drug substance specification. Change(s) to the test method(s) and/or specifications for the active substance	26/06/2008	30/06/2008		The Marketing Authorisation Holder applied for a revision of the drug substance specification.
IB/0010	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	15/05/2008	n/a	SmPC	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	26/02/2008	SmPC and PL	The MAH applied for a II variation for an update of section 4.8 of the SPC with the ADRs tongue disorder, face oedema, mouth oedema, hyperpigmentation of the skin and anaphylactic/allergic reactions and was submitted by the MAH upon request by the CHMP following the assessment of the 3rd PSUR. The Package Leaflet has been updated accordingly. Further, the MAH takes the opportunity to make some minor editorial changes to the SPC and Package Leaflet.
II/0005	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	26/04/2007	03/05/2007		

IB/0006	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	12/04/2007	n/a	SmPC and PL	
II/0004	Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	28/02/2007	SmPC and PL	The Marketing Authorisation Holder applied for a type II variation, upon request by the CHMP following the assessment of a Follow-Up Measure (FUM 016), to update section 5.3 of the SPC with information from a carcinogenicity study conducted in Transgenic rasH2 mice. In addition, the Marketing Authorisation Holder made minor editorial changes to the SPC and Package Leaflet and took the opportunity to add the contact details for Bulgaria and Romania to the list of local representatives in the Package Leaflet. This study showed that the frequency of two types of neoplastic lesions (lung adenoma and splenic haemangiosarcoma) was increased in mice treated with palifermin. However, the tumour frequency was within normal ranges of historical control data and there was no evidence of dose-response. It was concluded that these tumours were unlikely to be attributable to palifermin. The CHMP considers that evidence of carcinogenicity of palifermin was not indicated in this study conducted in Transgenic rasH2 mice. The Committee agreed with the MAH's proposal to update section 5.3 of the SPC to provide the information that no treatment related increases in the incidence of neoplastic lesions were observed in this carcinogenicity study.
II/0003	Update of or change(s) to the pharmaceutical documentation	21/09/2006	27/09/2006		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	03/05/2006	n/a	SmPC, Annex II, Labelling	

				and PL	
II/0001	Change(s) to shelf-life or storage conditions	23/03/2006	28/03/2006		