Dacogen

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/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2024		PL	
IB/0049	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/05/2024	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).

PSUSA/9118/202305	Periodic Safety Update EU Single assessment - decitabine	11/01/2024	n/a		PRAC Recommendation - maintenance
IAIN/0047	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	13/02/2023	n/a		
IB/0046	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/04/2022	n/a		
II/0044	Update of section 4.6 of the SmPC in order to update information on fertility, pregnancy and lactation, following PSUR procedure PSUSA/00009118/202005; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Italy in the Package Leaflet and to include some editorial changes in the PI to align with standard English spelling. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH	10/06/2021	29/06/2022	SmPC and PL	Due to the genotoxic potential of decitabine (see section 5.3), women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with Dacogen and for 6 months following completion of treatment. A pregnancy test should be performed on all women of childbearing potential before treatment is started.
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/05/2021	29/06/2022	PL	

PSUSA/9118/ 202005	Periodic Safety Update EU Single assessment - decitabine	28/01/2021	22/03/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9118/202005.
IA/0043/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.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	11/09/2020	n/a		
IB/0041	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2019	n/a		
IA/0040/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.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	08/08/2019	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0039	Update of the SmPC Section 4.8 to add "Hyperglycaemia" as a new adverse drug reaction with the frequency very common. As a result of this addition, the SmPC section 5.1 was also revised to delete sentence reporting hyperglycaemia frequency. 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	28/03/2019	24/03/2020	SmPC and PL	
PSUSA/9118/ 201805	Periodic Safety Update EU Single assessment - decitabine	13/12/2018	07/02/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9118/201805.
II/0033	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to reflect the results from paediatric study DACOGENAML2004, a phase 1-2 Safety and Efficacy Study of DACOGEN in sequential administration with Cytarabine in children aged 1 month to <18 years with relapsed or refractory acute myeloid leukemia, provided as per the requirement of article 46. The RMP version 3.3 (in line with the revision 2 of the RMP template) has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC to align the safety warning related to sodium excipient with the Annex to the revised European Commission guideline on `Excipients in the	13/12/2018	23/01/2019	SmPC and PL	A total of 17 subjects were enrolled in study DACOGENAML2004 and received DACOGEN 20 mg/m2 per day administered on Days 1 to 5 followed by cytarabine on Days 8 to 12 for up to 4 cycles.. Reported adverse events were consistent with the known safety profile of Dacogen in adults. No efficacy was observed in children aged 1 month to < 18 years with relapsed or refractory acute myeloid leukemia (AML). Of the 17 subjects enrolled in the study, 14 subjects died, the majority of these were due to disease progression. Therefore, the results of this study do not support a paediatric indication. Based on this, the SmPC has been updated with the results of the phase I/II paediatric study and to recommend that Dacogen should not be used in children with acute myeloid leukemia (AML)

	labelling and package leaflet of medicinal products for human use'. The Package Leaflet is updated accordingly. Moreover, the contact details of the local representative in Slovenia have been updated in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				aged < 18 years, because efficacy was not established.
II/0035	Update of section 4.4, and 4.8 of the SmPC in order to add the adverse events "Hepatic Function abnormal" with the frequency very common and "Hyperbilirubinaemia" with the frequency common, as well as to include clinical recommendations in patients developing signs or symptoms of hepatic impairment based on a cumulative review of post-marketing data and clinical literature; the Package Leaflet is updated accordingly. Moreover, the existing wording for the warning of patients with renal impairment has been revised in alignment with recommendation on patients with hepatic impairment. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of the local representative in Portugal in the Package Leaflet. Furthermore, the term "(for pH adjustment)" has been removed from the Annex IIIA in accordance with the revision 2 of the European Commission guideline on Excipients in the labelling and package leaflet of medicinal products for human	15/11/2018	07/02/2019	SmPC, Labelling and PL	Published literature identified 86 publications of which 18 evidenced changes in liver function tests, including hyperbilirubinemia, elevated AST/ALT and related hepatobiliary disorders. Moreover, severe elevated bilirubin and/or cholestatic events were observed, including severe LFT elevations with positive dechallenge. Based on this cumulative review, it is considered that hepatotoxicity with elevated LFT and bilirubine is associated with the use of decitabine. Therefore, changes to the product information of Dacogen are recommended in order to add the adverse events "hepatic function abnormal" with a frequency "very common", and "hyperbilirubinaemia" with a frequency "common" as new hepatobiliary disorders in section 4.8 of the SmPC. In addition, the existing warning for hepatic impairment is updated in section 4.4 of the SmPC to include clinical recommendations for patients who develop signs or symptoms.

	use. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2018	07/02/2019	PL	
IB/0036	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	31/07/2018	n/a		
II/0034/G	This was an application for a group of variations. 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.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	28/06/2018	n/a		
PSUSA/9118/ 201705	Periodic Safety Update EU Single assessment - decitabine	30/11/2017	n/a		PRAC Recommendation - maintenance

II/0031	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	24/08/2017	SmPC and PL	To bring Dacogen into compliance with the revised threshold for pyrogenic dose of bacterial endotoxins as defined in Chapter 5.1.10 'Guidelines for using the test for bacterial endotoxins' in edition 8.8 of the European Pharmacopoeia the concentration range of the final product for administration has been narrowed from '0.1 mg/ml-1.0 mg/ml' to '0.15 mg/ml-1.0 mg/ml' to comply with this recent Ph.Eur revision. Dacogen powder should be aseptically reconstituted with 10 ml of water for injections. Upon reconstitution, each ml contains approximately 5 mg of decitabine at pH 6.7 to 7.3. Within 15 minutes of reconstitution, the solution must be further diluted with cold infusion fluids (sodium chloride 9 mg/ml [0.9%] solution for injection or 5% glucose solution for injection) to a final concentration of 0.15 to 1.0 mg/ml. The posology and the method of administration are not changed as consequence of the change of the dilution.
R/0030	Renewal of the marketing authorisation.	23/03/2017	22/05/2017	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Dacogen in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/9118/ 201605	Periodic Safety Update EU Single assessment - decitabine	15/12/2016	23/02/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9118/201605.
IB/0029	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/11/2016	n/a		
II/0028/G	This was an application for a group of variations.	27/10/2016	23/02/2017	SmPC	

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products				
IB/0026	C.I.6.z - Change(s) to therapeutic indication(s) - Other variation	31/05/2016	30/06/2016	SmPC and PL	
IA/0025	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)	23/03/2016	n/a		
IB/0024	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/03/2016	n/a		
PSUSA/9118/ 201505	Periodic Safety Update EU Single assessment - decitabine	03/12/2015	n/a		PRAC Recommendation - maintenance
IB/0023/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are	14/10/2015	n/a		

	aseptically manufactured) excluding biological/ immunological medicinal products 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.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.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IB/0022	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/08/2015	n/a		
IB/0020/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the	19/05/2015	n/a		

	finished product - Tightening of specification limits B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation				
PSUSA/9118/ 201411	Periodic Safety Update EU Single assessment - decitabine	07/05/2015	n/a		PRAC Recommendation - maintenance
IB/0019/G	This was an application for a group of variations. B.II.f.1.a.3 - Stability of FP - Reduction of the shelf life of the finished product - After dilution or reconstitution B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.a.6 - Deletion of the solvent/diluent container from the pack	27/03/2015	07/03/2016	SmPC and PL	
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		
IA/0016/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	07/01/2015	n/a		
PSUV/0014	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance

IB/0013	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	11/09/2014	n/a		
IA/0015/G	This was an application for a group of variations. 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.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 originally approved batch size 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 originally approved batch size	09/09/2014	n/a		
PSUV/0011	Periodic Safety Update	22/05/2014	18/07/2014	SmPC and PL	Please refer to Dacogen PSUV-11 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0009	To add specification limits for a specified identified impurity to the release and shelf-life specifications of the finished product and to widen the specification limit for this impurity during shelf-life. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change	20/02/2014	n/a		

	outside the approved specifications limits range				
IB/0010	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	07/02/2014	n/a		
PSUV/0008	Periodic Safety Update	21/11/2013	16/01/2014	SmPC, Annex II and PL	Update of the SmPC to add a warning related to infections in section 4.4 and to add the adverse reaction "other infections (viral, bacterial, fungal)" with a frequency "very common" in section 4.8 based on the results of cumulative reviews performed by the MAH. The package leaflet was updated accordingly. Please refer to: Dacogen-H-C-2221-PSUV-0008 EPAR - Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IA/0007/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	15/10/2013	n/a		
IAIN/0006	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	27/09/2013	16/01/2014	SmPC and PL	
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and	31/07/2013	n/a		

	Veterinary Medicinal Products - Other variation				
N/0002	Adding "Cytotoxic" to the labeling - outer carton and vial label of Annex III. Notifying the inclusion of the marketing authorization number and the date of the authorization of the product. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/01/2013	16/01/2014	Labelling	
IB/0003/G	This was an application for a group of variations. 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.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	04/01/2013	n/a		
IAIN/0004	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	07/12/2012	n/a		
IAIN/0001	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/10/2012	n/a		