EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DepoCyte

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/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2017		Labelling and PL	
IA/0057	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	11/05/2016	n/a		
IA/0056	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	08/04/2016	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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	product formulation - Change that does not affect the product information				
IB/0055/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	22/03/2016	n/a		
PSUSA/911/201503	Periodic Safety Update EU Single assessment - cytarabine	03/12/2015	n/a		PRAC Recommendation - maintenance
IAIN/0054	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	16/07/2015	n/a		
IB/0052/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients	20/05/2015	26/05/2016	SmPC, Annex II, Labelling and PL	

IA/0051	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/04/2015	n/a		
IB/0050	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	05/11/2014	n/a		
IB/0049	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 aseptically manufactured) excluding biological/ immunological medicinal products	12/06/2014	n/a		
IA/0048	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	04/04/2014	n/a		
IA/0047/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	12/03/2014	n/a		

	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 batch control/testing takes place				
IB/0046/G	This was an application for a group of variations. B.II.a.3.b.6 - Changes in the composition (excipients) of the finished product - Other excipients - Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	24/01/2014	n/a		
IA/0045/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	24/04/2013	n/a		

IB/0044	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	12/02/2013	n/a		
N/0043	Update the information regarding the local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/11/2012	26/05/2016	PL	
IB/0042	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	31/05/2012	n/a		
IA/0041/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	12/10/2011	n/a		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/07/2011	n/a	PL	
R/0039	Renewal of the marketing authorisation.	17/03/2011	18/05/2011	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of DepoCyte continues to be favourable. The CHMP therefore recommended that a renewal can be

					granted with unlimited validity. The PSUR should be submitted on a 2 yearly cycle. In addition the CHMP recommended that the MAH should continue to closely monitor the following adverse reactions: infection and sepsis, leukoencephalopathy, arachnoiditis and Cauda Equina Syndrome.
IA/0038/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/11/2010	n/a		
II/0035	Update of sections 4.2, 4.4, 4.8 and 6.6 of the SPC, upon request by the CHMP following the assessment of 10th PSUR. The Package Leaflet (PL) has been updated accordingly. Furthermore, the list of local representatives in the PL has been revised to amend the contact details of the local representatives. Update of Summary of Product Characteristics and Package Leaflet	22/04/2010	04/06/2010	SmPC and PL	Further to the assessment of the 10th PSUR, the MAH was requested by the CHMP to update sections 4.4 and 4.8 of the SPC in order to include a warning related to the assessment of cerebrospinal fluid flow before treatment, and the adverse reaction of Cauda Equina Syndrome accordingly. Additionally, sections 4.2, 4.8 and 6.6 of the SPC and section 3 of the PL have been updated in order to ensure the correct use of dexamethasone. Finally, a cumulative review of 10 cases of leukoencephalopathy has been submitted and analysed by the MAH. The MAH committed that cases of leukoencephalopathy will be monitored weekly and cumulative review and discussion of this cases will be submitted in subsequent PSURs.

IB/0036	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	17/05/2010	n/a		
IA/0037	A.1 - Administrative change - Change in the name and/or address of the MAH	06/05/2010	n/a	SmPC, Labelling and PL	
II/0034	Transfer of 6 release tests for the finished product from the US to the EU batch release site Elimination of release tests for the finished product that appear to be unnecessary per recent regulatory guidance for the finished product Removal of release tests for the finished product performed in the US that are duplicated in the EU batch release site Quality changes	17/12/2009	20/01/2010		
II/0033	Change to the release specification at the time of commercial release and update of the in-vitro assay limits. Quality changes	25/06/2009	16/07/2009		
II/0031	Update of Summary of Product Characteristics Update of Summary of Product Characteristics	23/04/2009	28/05/2009	SmPC	This type II variation concerns an update of the SPC, upon request by CHMP following the assessment of PSU 012 and FU2 012.1, to make minor changes to the existing information in section 4.4 regarding the risk of permanent central nervous system toxicity.

					Cytarabine, when administered intrathecally, has been associated with nausea, vomiting and serious central nervous system toxicity which can lead to a permanent deficit, this includes blindness, myelopathy and other neurological toxicity.
IA/0032	IA_01_Change in the name and/or address of the marketing authorisation holder	25/03/2009	n/a	SmPC, Labelling and PL	
IB/0029	IB_38_c_Change in test procedure of finished product - other changes	15/10/2008	n/a		
IA/0030	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	02/10/2008	n/a		
IA/0028	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	14/03/2008	n/a	Annex II and PL	
IA/0027	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	14/03/2008	n/a		
T/0026	Transfer of Marketing Authorisation	23/11/2007	08/01/2008	SmPC, Labelling and PL	This application concerned a transfer of the Marketing Authorisation from SkyePharma PLC to Pacira Limited.
IA/0025	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/07/2007	n/a		
IA/0023	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		
IA/0022	IA_38_a_Change in test procedure of finished	04/06/2007	n/a		

	product - minor change to approved test procedure				
IA/0021	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		
IA/0020	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/06/2007	n/a		
II/0016	Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	08/01/2007	SmPC and PL	The Marketing Authorisation Holder applied for a type II variation, upon request by the CHMP following the assessment of the paediatric data provided as part of procedures `OTH 008' and `FU2 008.1', to revise sections 4.2 and 5.1 of the SPC with information on the use of DepoCyte in the paediatric population. Safety and efficacy in children have not been adequately demonstrated. DepoCyte is not recommended for use in children and adolescents until further data become available. In an open-label non-comparative dose escalation study in 18 paediatric patients (4 to 19 years) with leukaemic meningitis or neoplastic meningitis due to primary brain tumour, an intrathecal dose of 35 mg was identified as the maximum tolerated dose. In addition, the Marketing Authorisation Holder took the opportunity to update the list of local representatives in the Package Leaflet with the contact details for Bulgaria and Romania.
N/0017	Minor change in labelling or package leaflet not	15/11/2006	n/a	Labelling and	

	connected with the SPC (Art. 61.3 Notification)			PL	
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/09/2006	n/a	Labelling and PL	
R/0013	Renewal of the marketing authorisation.	27/04/2006	19/06/2006	SmPC, Labelling and PL	Grounds for one additional renewal: Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit/risk balance of DepoCyte remains positive, but considers that its safety profile is to be closely monitored for the following reasons: DepoCyte is indicated for the intrathecal treatment of lymphomatous meningitis, and has the potential to produce serious neurological toxicity. Commonly occurring symptoms are those associated with irritation of the meninges or arachnoiditis, such as headache, nausea, vomiting, fever, neck rigidity, neck pain, back pain and convulsions. Toxicity may be related to single doses or be cumulative from multiple dosing, may occur soon after injection or be delayed. For these reasons it is clearly essential that close vigilance is maintained. DepoCyte was authorised in the EU on 11 July 2001. However, the medicinal product was not launched on the European market until in the first quarter of 2004, so post-marketing experience in the EU is limited to two years at the time of this renewal. Therefore, the CHMP decided that the MAH should continue to submit yearly PSURs for the next three years, focusing on continued close monitoring of neurological adverse reactions. The PSUR frequency will be

					reviewed by the CHMP at the end of this period. Therefore, in view of the limited period of marketing during this assessment period and based upon the safety profile of DepoCyte, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IA/0014	IA_01_Change in the name and/or address of the marketing authorisation holder	20/02/2006	n/a	SmPC, Labelling and PL	
II/0012	Quality changes	26/01/2006	31/01/2006		
II/0011	Update of or change(s) to the pharmaceutical documentation	14/12/2005	22/12/2005		
II/0009	Quality changes	27/07/2005	02/08/2005		
IB/0006	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	02/06/2004	n/a	SmPC	
IA/0007	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	10/05/2004	n/a		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/12/2003	08/03/2004	PL	
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	22/10/2003	n/a	Annex II and PL	
I/0004	11b_Change in supplier of an intermediate compound used in manufacture of the active	22/10/2003	n/a		

	substance				
I/0003	25_Change in test procedures of the medicinal product	22/10/2003	n/a		
I/0002	04_Replacement of an excipient with a comparable excipient	22/10/2003	n/a		