TRISENOX

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/0080	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	25/05/2023		SmPC and PL	
IB/0079/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters	27/10/2022	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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	and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue 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				
IAIN/0078/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	18/05/2022	n/a		
IB/0077/G	This was an application for a group of variations. 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	22/02/2022	03/02/2023	SmPC, Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing 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) 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				
II/0076	Update of section 4.6 of the SmPC in order to update information on pregnancy and contraception in male patients following the decision and discussion made for EMEA/H/C/PSUSA/00000235/202009 and to add an appropriate period of abstinence for breastfeeding during use of Trisenox. The Package Leaflet is updated accordingly. 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	13/01/2022	03/02/2023	SmPC and PL	SmPC new text: Due to the genotoxic risk of arsenic compounds (see section 5.3), women of childbearing potential must use effective contraceptive measures during treatment with TRISENOX and for 6 months following completion of treatment. Men should use effective contraceptive measures and be advised to not father a child while receiving TRISENOX and for 3 months following completion of treatment. Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in breast feeding infants and children from TRISENOX, breast-feeding must be discontinued prior to and throughout administration, and for two weeks after the last dose. For more information, please refer to the Summary of Product Characteristics.
IB/0075/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	18/10/2021	n/a		

	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.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				
PSUSA/235/202009	Periodic Safety Update EU Single assessment - arsenic trioxide	10/06/2021	n/a		PRAC Recommendation - maintenance
IA/0074	A.7 - Administrative change - Deletion of manufacturing sites	26/02/2021	n/a		
IA/0072/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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/06/2020	n/a		
IB/0070/G	This was an application for a group of variations. 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	06/12/2019	n/a		

	an obsolete parameter) 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 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.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation 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				
IB/0071	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	07/11/2019	27/10/2020	SmPC, Labelling and PL	
X/0068	Annex I_2.(c) Change or addition of a new strength/potency	28/03/2019	27/05/2019	SmPC, Labelling and PL	
IAIN/0069/G	This was an application for a group of variations.	04/01/2019	27/05/2019	Annex II and	

	A.7 - Administrative change - Deletion of manufacturing sites 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			PL	
PSUSA/235/201709	Periodic Safety Update EU Single assessment - arsenic trioxide	31/05/2018	26/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/235/201709.
IB/0065	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	11/12/2017	n/a		
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	07/12/2017	30/04/2018	Annex II and PL	
IB/0064	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	12/09/2017	n/a		
II/0063/G	This was an application for a group of variations. 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 B.II.d.2.a - Change in test procedure for the finished	05/05/2017	30/04/2018	Annex II and PL	

	product - Minor changes to an approved test procedure B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation				
IB/0062/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	10/01/2017	n/a		

	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.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.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				
IB/0061	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/11/2016	n/a		
II/0058	Extension of Indication to include induction of remission, and consolidation in adult patients with newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) in combination with all trans retinoic acid (ATRA), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene for Trisenox. As a consequence, sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. A revised version of the RMP (version 1.3) has been approved	13/10/2016	14/11/2016	SmPC, Annex II and PL	Please refer to the Scientific Discussion Trisenox-II-58.

	as part of this application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0060/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.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.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	11/11/2016	n/a		

	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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0059/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	15/06/2016	n/a		
IAIN/0057/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	04/02/2016	n/a		

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IA/0055	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	09/10/2015	n/a		
IA/0054	A.7 - Administrative change - Deletion of manufacturing sites	09/10/2015	n/a		
PSUSA/235/201409	Periodic Safety Update EU Single assessment - arsenic trioxide	07/05/2015	n/a		PRAC Recommendation - maintenance
T/0052	Transfer of Marketing Authorisation	08/01/2015	30/01/2015	SmPC, Labelling and PL	
IA/0051	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)	27/05/2014	n/a		
IB/0050	To update the annexes to QRD version 9. In addition, minor linguistic errors within the translated texts (French, Bulgarian, German, Swedish, Romanian, Danish, Hungarian Greek, Czech, Spanish Estonian, Italian, Finnish, Slovakian Portuguese & Lithuanian) are being corrected.	13/05/2014	13/11/2014	SmPC, Annex II and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/01/2014	13/11/2014	Labelling	
IAIN/0048	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	19/11/2013	13/11/2014	Annex II and PL	
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2013	13/11/2014	Labelling and PL	
IAIN/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/08/2013	n/a		
T/0044	MA Transfer from Cephalon Europe to Teva Pharma B.V. Transfer of Marketing Authorisation	12/12/2012	28/01/2013	SmPC, Labelling and PL	
II/0043	Addition of an alternate manufacturing site of the active substance (Arsenic Trioxide). B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF	20/09/2012	20/09/2012		

II/0042	Update of section 4.8 of the SmPC in order to include lymphopenia, headache and increased gamma-glutamyltransferase in the tabulated list of adverse reactions based on the review of safety data collected during a non-Cephalon sponsored study conducted by the Cancer and Leukaemia Group B (CALGB) from 1999 to 2010 (CALGB study C9710). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to include changes to the Package leaflet following the results of user consultation with Target Patient Group (Final report dated 12 August 2011) and to update the list of local representatives in the Package Leaflet. Furthermore, the dilution process was clarified in the health care professional part of the Package Leaflet following reports of accidental exposure when opening the ampoules of Trisenox. Finally, the PI is being brought in line with the latest QRD template version 8 rev 1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	Following a review of the safety data collected in a non-Cephalon sponsored study conducted by the Cancer and Leukaemia Group B (CALGB) from 1999 to 2010 (CALGB study C9710) to evaluate Trisenox as consolidation treatment in newly diagnosed acute promyelocytic leukaemia (APL), the MAH identified 3 adverse events for inclusion in section 4.8 undesirable effects of the SmPC. Lymphopenia and increased gamma-glutamyltransferase are now listed with a frequency "not know" for all grades of severity and headache is listed with a frequency "very common" for all grades and "not known" for Grades≥3. The PL was updated accordingly.
II/0041	To update the product information in line with version 7.3.1 of the QRD template and the SmPC guideline. In addition, a re-analysis of the safety dataset was performed to specify the frequency of adverse drug reactions in section 4.8 of the SmPC. Furthermore, the MAH took the opportunity of this variation to introduce some minor editorial changes	20/10/2011	22/11/2011	SmPC, Annex II, Labelling and PL	The product information was updated in line with version 7.3.1 of the QRD template and with the SmPC guideline. A re-analysis of the safety database of the 2 Trisenox studies including 52 patients with relapsed/refractory APL was conducted to determine the frequencies of the undesirable effects listed in section 4.8 of the SmPC. Minor editorial changes to the product information were also introduced.

	to the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IB/0039	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	30/11/2010	n/a		
IA/0040	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	30/11/2010	n/a		
S/0036	Annual re-assessment.	20/05/2010	10/08/2010	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable. The CHMP considered that, as all specific obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances.
IB/0037	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)	11/05/2010	n/a	SmPC	

S/0033	Seventh Annual reassessment (S/033)	25/06/2009	21/09/2009	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances. Annex IIC has been amended according to the conclusions reached during the CHMP discussion.
IA/0035	IA_09_Deletion of manufacturing site	24/06/2009	n/a		
IA/0034	IA_09_Deletion of manufacturing site	23/06/2009	n/a		
II/0032	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	21/04/2009	SmPC and PL	This type II variation concerns an update of section 4.8 of the SPC with the ADRs 'pancytopenia' and 'differentiation syndrome' reported during post-marketing experience. A differentiation syndrome, like retinoic acid syndrome, has also been reported for the treatment of malignancies other than APL with Trisenox. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some minor editorial changes to the SPC and the Package Leaflet.
II/0031	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	21/04/2009	SmPC and PL	This type II variation concerns an update of sections 4.2, 4.4 and 5.2 of the SPC with further information regarding patients with renal and/or hepatic impairment in line with the results of the pharmacokinetic studies CTI-1064 and CTI-1073, and a general revision of the information on pharmacokinetics in section 5.2 of the SPC for increased clarity. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some

					minor editorial changes to the SPC and the Package Leaflet. Since only limited data are available across all hepatic impairment groups and across all renal impairment groups, caution is advised in the use of TRISENOX in patients with hepatic and/or renal impairment. The experience in patients with severe renal impairment is insufficient to determine if dose adjustment is required and the use of TRISENOX in patients on dialysis has not been studied. Similarly, the experience in patients with severe hepatic impairment is insufficient to determine if dose adjustment is required. Plasma clearance of AsIII was not altered in patients with mild renal impairment (creatinine clearance of 50-80 mL/min) or moderate renal impairment (creatinine clearance of 30-49 mL/min). The plasma clearance of AsIII in patients with severe renal impairment (creatinine clearance less than 30 mL/min) was 40% lower when compared with patients with normal renal function. Systemic exposure to MMAV and DMAV tended to be larger in patients with renal impairment; the clinical consequence of this is unknown but no increased toxicity was noted. Pharmacokinetic data from patients with hepatocellular carcinoma having mild to moderate hepatic impairment indicate that AsIII or AsV do not accumulate following twice-weekly infusions. No clear trend toward an increase in systemic exposure to AsIII, AsV, MMAV or DMAV was observed with decreasing level of hepatic function as assessed by dose-normalized (per mg dose) AUC.

S/0029	Sixth Annual Reassessment (S/029)	30/05/2008	25/07/2008	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances. Annex IIC has been amended according to the conclusions reached during the CHMP discussion.
IA/0030	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	09/04/2008	n/a		
IA/0028	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	10/03/2008	n/a		
S/0026	Annual re-assessment.	24/05/2007	23/07/2007	Annex II	On the basis of the submitted data, the CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances.
T/0027	Transfer of Marketing Authorisation	02/05/2007	05/06/2007	SmPC, Labelling and PL	The MAH applied for the transfer of the Marketing Authorisation of Trisenox from Cephalon UK Ltd to Cephalon Europe.
II/0025	Update of or change(s) to the pharmaceutical documentation	26/04/2007	03/05/2007		

R/0021	Renewal of the marketing authorisation.	14/12/2006	15/02/2007	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 Trisenox continues to be favourable. In the absence of specific safety problems, given the stability of the population exposed to Trisenox, and the fact that section 4.8 of the SPC has been recently updated, the MAH can hereby change to a 3-year PSUR cycle. The CHMP recommends a renewal of the Marketing Authorisation for Trisenox under exceptional circumstances. The outstanding clinical data that will be generated by the ongoing studies, included as part of the Specific Obligations, will provide additional pharmacokinetic and/or efficacy information. There are therefore no specific safety/ pharmacovigilance concerns, which would require a further renewal. Therefore, the CHMP is of the opinion that the renewal can be granted with unlimited validity. During the renewal procedure, changes were made to the Product Information to bring it in line with the current EMEA/QRD template, SPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.
IA/0024	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	15/02/2007	n/a		

IA/0023	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	15/02/2007	n/a		
IA/0022	IA_05_Change in the name and/or address of a manufacturer of the finished product	17/01/2007	n/a	Annex II and PL	
S/0017	Annual re-assessment.	01/06/2006	11/07/2006	Annex II	On the basis of the submitted data, the CHMP, having reviewed the compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, is of the opinion that the quality, safety and efficacy continues to be to be favourable for Trisenox in the approved indication. It is recommended that the marketing authorization remain under exceptional circumstances.
IA/0020	IA_37_a_Change in the specification of the finished product - tightening of specification limits	09/06/2006	n/a		
IA/0019	IA_05_Change in the name and/or address of a manufacturer of the finished product	09/06/2006	n/a		
IA/0018	IA_37_a_Change in the specification of the finished product - tightening of specification limits	09/06/2006	n/a		
T/0016	Transfer of Marketing Authorisation	03/03/2006	24/04/2006	SmPC, Labelling and PL	The MAH applied for the transfer of the Marketing Authorisation of Trisenox from Cell Therapeutics UK Ltd to Cephalon UK Ltd.
S/0015	Annual re-assessment.	23/06/2005	06/10/2005	Annex II	On the basis of the submitted data, the CHMP, having reviewed the compliance with the specific obligations submitted by the MAH and having re-assessed the

					benefit/risk profile of the medicinal product, is of the opinion that the quality, safety and efficacy continues to be to be favorable for Trisenox in the approved indication. It is recommended that the marketing authorization remain under exceptional circumstances.
II/0014	Update of Summary of Product Characteristics and Package Leaflet	26/05/2005	04/07/2005	SmPC and PL	The MAH applied for the following changes to the SPC, as requested by the CHMP following the assessment of 3rd and 4th PSURs: Section 4.4, addition of "Leukocyte Activation Syndrome"; Section 4.8, update the overall adverse events; Section 4.9, inclusion of the current recommendations for treatment of arsenic overdose (Merck Manual); Section 5.2, inclusion of a statement on in vitro P450 enzyme interactions. The Package Leaflet was updated accordingly. Editorial and spelling corrections have been implemented in the SPC and Package Leaflet.
II/0012	Quality changes	18/11/2004	24/11/2004		
S/0013	Annual re-assessment.	03/06/2004	09/09/2004	Annex II	
IB/0008	IB_17_a_Change in re-test period of the active substance	24/03/2004	n/a		
IA/0010	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	10/03/2004	n/a		
IA/0009	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	10/03/2004	n/a		
IA/0011	IA_12_a_Change in spec. of active subst./agent used	09/03/2004	n/a		

	in manuf. of active subst. - tightening of spec.				
IA/0007	IA_37_a_Change in the specification of the finished product - tightening of specification limits	09/03/2004	n/a		
IA/0006	IA_05_Change in the name and/or address of a manufacturer of the finished product	23/02/2004	n/a	Annex II and PL	
IB/0005	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	04/02/2004	n/a	SmPC	
IA/0004	IA_05_Change in the name and/or address of a manufacturer of the finished product	07/01/2004	n/a	Annex II and PL	
S/0003	Annual re-assessment.	26/06/2003	08/10/2003	Annex II	
I/0002	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	18/09/2002	24/09/2002		
I/0001	03_Change in the name and/or address of the marketing authorisation holder	11/04/2002	23/05/2002	SmPC, Labelling and PL	