EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Zerit

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision [2] issued / amended on	Product Information affected [3]	Summary
PSUSA/2787/201806	Periodic Safety Update EU Single assessment - stavudine	14/02/2019	n/a		PRAC Recommendation - maintenance
IAIN/0107	A.1 - Administrative change - Change in the name and/or address of the MAH	28/02/2019		SmPC, Labelling and PL	
IAIN/0106	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018		SmPC	

[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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IA/0104	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)	02/10/2018	n/a		
PSUSA/2787/ 201606	Periodic Safety Update EU Single assessment - stavudine	09/02/2017	n/a		PRAC Recommendation - maintenance
IB/0101	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2016	11/09/2017	SmPC and PL	
IA/0102/G	This was an application for a group of variations. 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	22/09/2016	n/a		
II/0099	C.I.3.z - 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 - Other variation	21/04/2016	11/05/2016	SmPC, Annex II, Labelling and PL	Co-administration with didanosine is contraindicated due to the potential for serious and/or life-threatening events notably lactic acidosis, liver function abnormalities, pancreatitis and peripheral neuropathy. The combination of stavudine with didanosine is contraindicated given that both drugs exhibit high risk of mitochondrial toxicity.
IB/0100/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters	18/03/2016	n/a		

	and/or limits of the finished product - Tightening of specification limits 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.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				
IB/0098/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	14/01/2016	11/05/2016	SmPC and PL	
IG/0602	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)	11/09/2015	n/a		
IA/0096	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)	16/07/2015	n/a		
IA/0095	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/02/2015	n/a		

PSUSA/2787/201406	Periodic Safety Update EU Single assessment - stavudine	12/02/2015	n/a		PRAC Recommendation on maintenance
IA/0093	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	23/09/2014	n/a		
IAIN/0092/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.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	01/07/2014	16/03/2015	Annex II and PL	
N/0091	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/06/2014	16/03/2015	PL	
IA/0090	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	28/03/2014	n/a		
WS/0539	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC to revise the wording regarding the risk of sexual transmission of	20/03/2014	16/03/2015	SmPC and PL	During recent years conclusive evidence has been collected which shows that the risk for HIV patients, who are well treated, to sexually transmit HIV to their partner is exceedingly low. A position statement on the use of antiretroviral therapy to reduce HIV transmission was published by the British HIV Association (BHIVA) in January

	HIV infection following CHMP request adopted in December 2013. The PL has been updated accordingly. In addition, the MAH took the opportunity to update the details of the local representatives for Croatia and to incorporate the Croatian language annexes for Zerit. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				2013. As a consequence, the recommendations for post-exposure prophylaxis have also been changed in recently updated HIV treatment guidelines. For example, the 2013 BHIVA guideline does not generally recommend post-exposure prophylaxis (PEP) after exposure from a partner with well treated HIV. Based on these data, the wording on the risk of transmission for HIV products was revised to reflect the current scientific knowledge.
IB/0086	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/12/2013	n/a		Update of the RMP to include the Immune Reconstitution Syndrome (IRS) as a potential risk in line with the CHMP class labelling request. Of note, the Product Information for Zerit has been updated accordingly (WS/0388 opinion issued 30 May 2013).
IA/0087	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	12/12/2013	n/a		
IA/0088	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	09/12/2013	n/a		
WS/0388	This was an application for a variation following a worksharing procedure according to Article 30 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding autoimmune disorders in relation to Immune Reactivation	30/05/2013	21/06/2013	SmPC and PL	Upon review of safety data and literature on immune disorders in association with antitretrovirals for the treatment of HIV, the CHMP considered that there is sufficient evidence to conclude that immune reconstitution syndrome (IRS) after antiretroviral therapy may be associated with autoimmune disease/disorders even if the number of case reports is limited. Therefore, the CHMP had

	Syndrome, following a class labelling for antiretrovirals as requested by the CHMP. The PL was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL. 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				requested the inclusion of information on immune disorders under immune reconstitution as a class labelling for all antiretrovirals for the treatment of HIV.
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0083/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.7 - Administrative change - Deletion of manufacturing sites	24/05/2012	n/a		
IA/0082	A.7 - Administrative change - Deletion of manufacturing sites	25/11/2011	n/a		
R/0079	Renewal of the marketing authorisation	17/02/2011	20/04/2011	SmPC, Annex II, Labelling and PL	In the light of the mitochondrial toxicity related to the use of stavudine, the indication has been restricted to the sole cases when other antiretroviral therapies can not be used. In addition, given that the toxicity of stavudine appears with its long term use, the duration of therapy with stavudine has

					been limited to shortest time possible. The treatment with stavudine should be followed by a switch to an alternative appropriate therapy whenever possible and the patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible. The CHMP requested the submission of a Risk Management Plan (RMP) which includes the conduct of a Drug Utilisation Study (DUS) in order to ensure that the restricted indication and duration of treatment is respected in practice by the physicians.
IA/0081	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	25/03/2011	n/a		
II/0080	In fulfilment of FUM 54, an update of Section 4.8 of the SmPC with the re-evaluated frequencies of those adverse drug reactions, which are currently categorized as "frequency not known", in accordance to the SmPC-Guideline (Rev.2,September 2009) is proposed. Updates of the PL in line with these changes are proposed. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	18/03/2011	SmPC and PL	The MAH re-evaluated the frequencies of those adverse drug reactions, which are currently categorized as "frequency not known" taking into accounts the recommendations of the SmPC-Guideline (Rev.2). Revisions of section 4.8 of the SmPC were made to show the following frequencies: Anaemia- Rare, Thrombocytopenia- Very rare, Neutropenia- Very rare, Diabetes mellitus- Very rare, Hyperglycaemia- Rare, Motor weakness- Very rare, Liver failure- Very rare, Hepatic steatosis- Rare. Changes to the PL were made accordingly.
IA/0078	A.7 - Administrative change - Deletion of manufacturing sites	29/09/2010	n/a	Annex II and PL	

IA/0077/G	This was an application for a group of variations. 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 C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	09/09/2010	n/a	Annex II	
II/0075	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.8 of the SmPC regarding a lipoatrophy effect in HIV-infected patient for consistency with stavudine CCDS. The PL has been updated accordingly. Furthermore the MAH took the opportunity to update sections 4.6 and 4.8 of the SmPC to be in line with the SmPC guideline. The local representative of Cyprus has also been updated in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	06/09/2010	SmPC and PL	Update of sections 4.4 and 4.8 regarding the "lipodystrophy syndrome" potentially linked to a mitochondrial toxicity. In addition, it has been raised that stavudine also carries a risk for lactic acidosis in the order of 1%. Therefore lactic acidosos has been moved from unknowm to uncommon in the tabulated Summary of the Adverse Drug Reactions in the section 4.8.
IB/0076	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	12/08/2010	n/a	SmPC, Labelling and PL	

IA/0074/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.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	19/03/2010	n/a	Annex II	
II/0073	To add an alternate site for manufacturing of Zerit capsules and primary packaging of the capsules in bottles. Quality changes	17/12/2009	06/01/2010		
II/0072	To update section 4.8 of the SPC to add a paragraph regarding motor weakness and to add the adverse reactions: anaemia, neutropenia, diabetes mellitus & hyperglycaemia. Section 4 of the PL is updated accordingly. The MAH took the opportunity of this change to update the contact details for the Estonian local representative. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	28/10/2009	SmPC and PL	The MAH has performed a comprehensive, cumulative search of the MAH's safety database to identify all spontaneous and literature reports in which stavudine was considered a suspect or interacting drug. As a result of the evaluation of these data the following adverse reactions: anaemia, neutropenia, diabetes mellitus & hyperglycaemia were added to section 4.8 "Undesirable effects" on postmarketing experience. Furthermore, a paragraph was included concerning rare reports of motor weakness in patients receiving combination antiretroviral therapy with most of the cases occurring in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome.
II/0066	To update section 5.2 of the SPC with the results of the study AI455-141 on pharmacokinetics and metabolism in healthy subjects. The MAH took the	23/07/2009	28/08/2009	SmPC and PL	Study AI455-141 provided information on pharmacokinetics, metabolism, routes of elimination and extent of elimination of a single oral dose of 80 mg stavudine in healthy persons.

	opportunity of this variation to reformat section 5.1 according to the CHMP Guidance on the Clinical Development of Medicinal Products for the Treatment of HIV Infection. The MAH also took the opportunity to update the contact details of the Belgian local representative in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet				The main result of the study was that the major amount of stavudine (about 70% of dose) is eliminated renally as unchanged stavudine in urine. This significantly differs from existing data on metabolism in HIV-infected patients. In HIV-infected patients, the absolute amount of stavudine that is eliminated as unchanged substance in the urine is in the same range as in healthy persons. Though, the overall excretion is higher due to other additional ways of elimination. The fraction of a dose that is eliminated renally as unchanged substance is only about 40 %. The reasons for this phenomenon remain unknown. These results were reflected in the SPC. The new data does not question the proposed dose adjustments for renally impaired patients, who should always be monitored carefully.
II/0071	to add the BMS facility in Mount Vernon (USA) as an alternate site for manufacturing and primary packaging Quality changes	23/07/2009	28/08/2009		
IA/0070	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/03/2009	n/a		
IA/0069	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	10/03/2009	n/a		
IA/0068	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR, incl. QC/testing	10/03/2009	n/a	Annex II and PL	
II/0067	Update of the Detailed Description of	22/01/2009	25/02/2009	Annex II	Annex II was updated to introduce the relevant sentence

	Pharmacovigilance System (DDPS) version 3.0. Annex IIB was amended accordingly. Changes to QPPV Update of DDPS (Pharmacovigilance)				regarding the pharmacovigilance system.
II/0063	The MAH applied to reformat and update the drug product quality information for Zerit Capsules into CTD. Quality changes	18/12/2008	05/01/2009		
II/0062	The MAH has applied for an updated description to the manufacturing process for stavudine drug substance. Quality changes	23/10/2008	03/11/2008		
IB/0065	IB_37_b_Change in the specification of the finished product - add. of new test parameter IB_38_c_Change in test procedure of finished product - other changes	04/09/2008	n/a		
IB/0064	IB_37_b_Change in the specification of the finished product - add. of new test parameter IB_38_c_Change in test procedure of finished product - other changes	04/09/2008	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/2008	n/a	PL	
IB/0059	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	31/01/2008	n/a		

IB/0058	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	31/01/2008	n/a		
IA/0060	IA_13_a_Change in test proc. for active substance - minor change	18/12/2007	n/a		
IA/0057	IA_13_a_Change in test proc. for active substance - minor change	14/11/2007	n/a		
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2007	n/a		
IB/0056	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	24/04/2007	n/a		
IA/0054	IA_39_Change/addition of imprints, bossing or other markings	16/03/2007	n/a		
II/0052	Update of section 4.4 and section 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. In addition the MAH completed the list of local representatives in the PL to include the two EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD template. The contact details for the local representatives in Estonia, Greece, Iceland, Latvia and Lithuania have been updated.	14/12/2006	19/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches

	Update of Summary of Product Characteristics and Package Leaflet				and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
IA/0053	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	18/12/2006	n/a		
IB/0051	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	16/10/2006	n/a		
IB/0050	IB_10_Minor change in the manufacturing process of the active substance	16/10/2006	n/a		
R/0046	Renewal of the marketing authorisation.	26/01/2006	10/04/2006	SmPC, Annex II, Labelling and PL	
IB/0049	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	03/03/2006	n/a		
IB/0048	IB_10_Minor change in the manufacturing process of the active substance	01/03/2006	n/a		
IB/0047	IB_10_Minor change in the manufacturing process of the active substance	01/02/2006	n/a		
II/0044	To update sections 4.4 “Special warnings and special precautions for use” and 4.8 “Undesirable effects” of the Summary of Product Characteristics (SPC) to include a statement on the increased risk of pancreatitis (fatal and non-fatal), fatal hepatic events and peripheral neuropathy (severe in some cases) in	27/07/2005	31/08/2005	SmPC and PL	

	HIV infected patients receiving stavudine in association with hydroxyurea and didanosine. In addition, the Marketing Authorisation Holder (MAH) took the opportunity of this variation to update section 9 “Date of first authorisation/renewal of the authorisation” of the SPC according to the current template and to update the contacts of the local representatives in Germany, France and Island in the Package Leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet				
IA/0045	IA_01_Change in the name and/or address of the marketing authorisation holder	09/08/2005	n/a	SmPC, Labelling and PL	
IA/0043	IA_47_a_Deletion of a pharmaceutical form	17/03/2005	n/a	SmPC, Labelling and PL	
II/0040	To update section 4.4 "Special warnings and special precautions for use" and section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) and section 2 “Before you take Zerit” of the Package Leaflet (PL), to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/11/2004	20/01/2005	SmPC, Labelling and PL	

II/0039	To update section 4.8 “Undesirable effects” of the Summary of Product Characteristics (SPC), to include hyperlactatemia in the postmarketing section, following assessment of PSUR 10 covering the period 24/12/2002-23/12/2003. Update of Summary of Product Characteristics	18/11/2004	20/01/2005	SmPC	
IA/0042	IA_32_a_Change in batch size of the finished product - up to 10-fold	12/01/2005	n/a		
IA/0041	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	29/11/2004	n/a		
N/0038	To amend the list of local representatives in the Package Leaflet, namely to correct the address of the representatives in France, Latvia, and Republic of Slovenia. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/06/2004	n/a	PL	
II/0037	Update of the section 4.4 (Special warnings and special precaution for use) of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) under subheading "Pregnancy" , to implement the class labelling for nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) regarding mitochondrial toxicity in children with in utero and post-natal exposure, as adopted by the CPMP in November 2003. In addition, the MAH has taken the opportunity to introduce minor linguistic	24/03/2004	28/04/2004	SmPC and PL	

	changes in the Greek, Portuguese, Spanish and Norwegian language versions. For the Greek versions "stavudine" has been translated into Greek. Update of Summary of Product Characteristics and Package Leaflet				
II/0036	Update of the sections 4.4 "Special warnings and special precautions of use" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics (SPC) to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products in April 2003. Relevant changes are equally proposed for the Package Leaflet (PL). Furthermore, the MAH has taken this opportunity to update the section 4.2."Posology and method of administration" of the SPC to revise the paragraph on dose adjustment in case of peripheral neuropathy further to the CPMP assessment of variation II/33, and to update section 4.8 "Undesirable effects" to include macrocystosis further to the CPMP assessement of the PSURs, covering the period November 2000 - December 2001 and December 2001 - December 2002, respectively. Also, the MAH has updated the PL in section 4 to revise the wording on lipodystrophy as adopted by the CPMP in March 2003. Finally, the MAH has further harmonised the wording of the SPC and PL of the prolonged-release and immediate release formulations. Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	27/01/2004	SmPC and PL	

II/0034	The Marketing Authorisation Holder (MAH) applied for an extension of indication for Zerit hard capsules and Zerit powder for oral solution to include newborns based on new clinical data. Changes relate to sections 4.1 ("Therapeutic indications), 4.2 ("Posology and method of administration"), 4.4 ("Special warnings and special precautions for use"), 4.6 ("Pregnancy and lactation"), 4.8 ("Undesirable Effects"), 5.1 ("Pharmacodynamic properties"), 5.2 ("Pharmacokinetic properties"), 5.3 ("Preclinical Safety data") and 6.6 ("Instructions for use and handling and disposal"). Relevant changes are equally proposed for the Package Leaflet (PL). In addition, the list of local representatives in the PL has been revised. Extension of Indication	24/07/2003	24/10/2003	SmPC and PL	
II/0035	The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics to include the class labelling on Lipodystrophy in sections 4.4 (" Special warnings and special precautions for use") and 4.8 ("Undesirable Effects"). Relevant changes are equally proposed for the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	30/06/2003	SmPC and PL	
II/0033	The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics (SPC) to harmonise the SPC of the immediate release	23/01/2003	16/05/2003	SmPC and PL	

	formulations with the SPC for Zerit prolonged-release hard capsules. Changes relate to sections 4.1 (“Therapeutic indications), 4.2 (“Posology and method of administration”), 4.3 (“Contra-indications”), 4.4 (“ Special warnings and special precautions for use”), 4.5 (“ Interactions with other medicinal products and other forms of interaction”), 4.6 (“ Pregnancy and lactation”), 4.8 (“Undesirable Effects”), 5.1 (“Pharmacodynamic properties”), 5.2 (“Pharmacokinetic properties”), 6.1 (“List of excipients”). Furthermore, section 4.8 of the SPC of the Zerit immediate release formulations and Zerit prolonged-release hard-capsules has been revised according to the SPC guideline. Relevant changes are equally proposed for the Package Leaflet (PL). In addition, the list of local representatives in the PL of the Zerit immediate release formulations and Zerit prolonged-release hard-capsules has been revised. Update of Summary of Product Characteristics and Package Leaflet				
X/0028	X-3-iii_Addition of new strength	25/07/2002	12/11/2002	SmPC, Annex II, Labelling and PL	
N/0032	Minor change in labelling or package leaflet, not connected with the SPC (Art. 61.3 Notification)	30/10/2002	20/11/2002	PL	
I/0031	04_Replacement of an excipient with a comparable excipient	06/08/2002	10/09/2002		

N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/06/2002	28/06/2002	PL	
I/0029	20a_Extension of shelf-life or retest period of the active substance	25/01/2002	04/02/2002		
II/0026	Update of Summary of Product Characteristics and Package Leaflet	20/09/2001	30/01/2002	SmPC and PL	The Marketing Authorisation Holder applied for a variation to update section 4.4 (Special warnings and special precautions for use) in the Summary of Product Characteristics and relevant sections of the Package Leaflet due to reports of following reports of sometimes fatal, progressive ascending muscular weakness in association with lactic acidosis, among patients receiving stavudine.
I/0027	03_Change in the name and/or address of the marketing authorisation holder	05/10/2001	21/11/2001	SmPC, Labelling and PL	
II/0021	Update of Summary of Product Characteristics and Package Leaflet	29/03/2001	25/07/2001	SmPC and PL	The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics, (sections “Special warnings and special precautions for use” and “Undesirable effects”, and as a consequence an update of the Package Leaflet). Furthermore, the MAH proposed some minor changes in the SPC and Package Leaflet in order to bring the text in line with the latest QRD/ EMEA templates.
II/0023	Change(s) to the manufacturing process of the active substance	31/05/2001	21/06/2001		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/12/2000	22/01/2001	PL	
N/0019	Minor change in labelling or package leaflet not	09/06/2000	24/07/2000	PL	

	connected with the SPC (Art. 61.3 Notification)				
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/04/2000	31/05/2000	PL	
II/0014	Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/09/1999	21/02/2000	SmPC, Labelling and PL	
I/0017	16_Change in the batch size of finished product	08/10/1999	14/10/1999		
I/0016	15_Minor changes in manufacture of the medicinal product	08/10/1999	14/10/1999		
I/0015	12_Minor change of manufacturing process of the active substance	16/07/1999	27/07/1999		
II/0012	Change(s) to the manufacturing process for the active substance	21/10/1998	21/10/1998		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/09/1998	09/10/1998	PL	
I/0011	16_Change in the batch size of finished product	11/05/1998	n/a		
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/1998	03/04/1998	PL	
II/0008	Update of Summary of Product Characteristics	24/09/1997	12/12/1997	SmPC	The Marketing Authorisation Holder applied for the update of the safety sections of the Summary of Product Characteristics with regard to the occurrence of cases of lactic acidosis and to the mention of some undesirable

					effects.
I/0009	12_Minor change of manufacturing process of the active substance	25/09/1997	n/a		
II/0005	Extension of Indication	16/04/1997	28/07/1997		
II/0004	Update of Summary of Product Characteristics	17/10/1996	03/02/1997		
I/0003	16_Change in the batch size of finished product	07/11/1996	n/a		
I/0002	01_Change following modification(s) of the manufacturing authorisation(s)	16/10/1996	n/a		