EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

Zerit

stavudine

Procedure No.: EMEA/H/C/000110/R/0079

Note

Renewal assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Evaluation of Medicines for Human Use

CHMP renewal assessment report

Zerit

(stavudine)

EMEA/H/C/000110/R/0079

Marketing Authorisation Holder (MAH): Bristol-Myers Squibb Pharma EEIG

1. Background information on the renewal

1.1. Marketing authorisation

The European Commission granted the Marketing Authorisation for Zerit on 9th May 1996 based on a favourable opinion adopted by the CHMP on 16th January 1996.

On 13th April 2006 the European Commission issued a Decision on the Renewal of the Marketing Authorisation. The need for an additional renewal was based on the following pharmacovigilance grounds: "*In view of the serious safety profile of Zerit in respect to mitochondrial toxicity and taking into consideration the still ongoing clinical studies with stavudine that may yield new safety data and have an influence on the benefit risk balance of the product, the CHMP considers that another renewal in 5 years is warranted*."

1.2. Steps taken after the granting of the Marketing Authorisation / last renewal

Subsequent to the granting of the Marketing Authorisation, the following changes were approved: A bulleted list of all variations / Extension of Marketing Authorisation Applications since last renewal is attached.

In addition, the Marketing Authorisation Holder has fulfilled the following follow-up measures (FUM): A bulleted list of all fulfilled FUMs since initial MA or last renewal is attached.

FUM 53 and FU2 44.1 were outstanding at the time at the time of the submission of this renewal.

1.3. Renewal application

Pursuant to Article 14 (1-3) of Regulation (EC) No 726/2004, the Marketing Authorisation Holder (MAH) Bristol-Myers Squibb Pharma EEIG, submitted to the Agency on 08 September 2010 an application for renewal of the Marketing Authorisation for Zerit. The expiry date of the Marketing Authorisation is 9th May 2011.

In fulfilment of FUM 53, the MAH submitted the following information as part of the renewal application:

- a review of lactic acidosis and polyneuropathy and an integrated discussion on these serious side effects in the benefit/risk section,
- an identification of the patients in need for stavudine, having in mind the options of antiretroviral therapy available,
- sales data on stavudine, more specifically providing PY of treatment sold over time, and sales pattern by country within the EU market at present.

Rapporteur: Tomas Salmonson
Co-Rapporteur: Jean-Louis Robert

Steps taken for the assessment of the renewal:

The Marketing Authorisation Holder submitted an application for renewal of the Marketing Authorisation on:	08 September 2010
The procedure started on:	19 September 2010
The Rapporteur's and Co-Rapporteur's preliminary joint assessment report was circulated to all CHMP Members on:	9 November 2010
The Rapporteur's and Co-Rapporteur's updated joint assessment report was circulated to all CHMP Members on:	9 December 2010
The CHMP, during its December 2010 plenary meeting, issued a request for supplementary information (RSI) on:	16 December 2010
The Marketing Authorisation Holder submitted the responses to the RSI on:	14 January 2011
The Rapporteur's and Co-Rapporteur's joint assessment report was circulated to all CHMP Members on:	21 January 2011
HIV / AV SAG met on:	3 February 2011
The Rapporteur's and Co-Rapporteur's updated joint assessment report was circulated to all CHMP Members on:	9 February 2011
The Rapporteur's and Co-Rapporteur's joint assessment report after HIV-SAG was circulated to all CHMP Members on:	11 February 2011
The Rapporteur's and Co-Rapporteur's Final joint assessment report was circulated to all CHMP Members on:	17 February 2011
The CHMP, during its February 2011 plenary meeting, issued a positive Opinion on the renewal of the Marketing Authorisation on:	17 February 2011

2. Scientific discussion

2.1. Introduction

The active substance in Zerit is stavudine (d4T) which is a nucleoside reverse transcriptase inhibitor (NRTI). It is licensed for use in combination with other antiretroviral medicinal products for the treatment of HIV infected patients.

Stavudine acts as a thymidine analogue which is phosphorylated by cellular kinases to d4T triphosphate competing with the natural substrate, thymidine triphosphate to inhibit HIV reverse transcriptase.

Stavudine also inhibits viral DNA synthesis by causing DNA chain termination due to a lack of the 3'-hydroxyl group necessary for DNA elongation.

Stavudine is available as 15 mg, 20 mg, 30 mg and 40 mg hard capsules and 200 mg powder for oral solution (1 mg/ml when reconstituted).

In the EU, d4T has been marketed in 20 member states and Norway during the reporting period.

The total number of patients exposed in the EU during the reporting period of 24 June 2005 through 23 June 2010 is estimated to be 56,311.

2.2. Quality

The MAH has confirmed that the quality, with respect to the method of preparation and control, has been regularly updated by variations to take account of technical and scientific progress in accordance with article 16(1) of Regulation (EC) No 726/2004 and that the product conforms to current CHMP quality guidelines.

The MAH provided current active substance specifications together with the composition and specifications for both finished product formulations - powder for oral solution and hard capsule (four strengths).

Since the last renewal, a number of variations have been submitted to update Module 3 of the dossier. A new manufacturer of the active substance was introduced. Several substantial changes were made to the active substance manufacturing process resulting in its improved overall quality. In-process control methods and release testing methods for the active substance control were modified. Minor changes occurred in the active substance packaging.

While the composition of the powder for oral solution remained unchanged since the last renewal, composition of the capsule shells and printing ink was modified for hard gelatine capsules. Manufacture of the finished product has been discontinued at two of the manufacturing sites for the finished product; these sites were removed from the dossier. On the other hand, a manufacturing facility for manufacture and primary packaging of the finished product was added. An alternative site for quality control testing, primary packaging, secondary packaging and batch release of the finished product was added, too. Manufacturing process for stavudine capsules was updated and new in-process controls were introduced. Specifications of both dosage forms of the finished product were amended to comply with the requirements of the Ph.Eur. Analytical methods for the finished product control were also modified. There was a change in storage conditions of the hard gelatine capsules.

No Quality Follow-Up Measures were introduced since 2004. Currently there is no outstanding Quality Follow-Up Measure for stavudine.

All the relevant sites of manufacture and testing are undergoing regular GMP inspections by an EEA competent authority or MRA partner authority and satisfactory GMP compliance of these sites has been confirmed by the MAH by submission of the appropriate documentation.

Appropriate declarations have been submitted concerning the GMP compliance status of the active substance manufacturer(s).

The quality of this product continues to be considered acceptable.

2.3. Non-clinical

The MAH submitted a non clinical overview which included the results of the literature review as well as results from internal studies conducted during the past 5 years with d4T.

Three internal studies were discussed regarding tissue distribution (Tissue distribution of radioactivity in male Long-Evans rats following oral administration of [14C] BMY-27857) and other toxicity studies [BMY-27857: Effect of combinations of nucleoside reverse transcriptase inhibitors on cell survival and mitochondrial DNA in cultured human hepatoma cells (HepG2) (Study DT05161) and BMY-27857: 6 week study in ob/ob mice (Study DT05118)].

A review of the published literature from June 2005 to June 2010 for d4T-related articles was conducted by the MAH using 4 databases: PubMed, Embase, Derwent Drug File, and BIOSIS. Search keywords included the following: stavudine, animal, preclinical, nonclinical, in vitro, pharmacokinetics, metabolism, distribution, excretion, elimination, enzyme inhibition, enzyme induction, absorption, clearance, and half life.

The published studies were conducted in various species and have confirmed the mitochondrial toxicity previously reported. Hence, the CHMP concluded that, overall, there was no previously unknown information that could be used to overcome the problems associated with mitochondrial toxicity. The nonclinical profile of d4T is well characterized, and information regarding its profile is provided in the current label.

2.4. Clinical efficacy and safety

2.4.1. Clinical efficacy

Since the last 5-year renewal, clinical study reports (CSRs) have been completed for 6 MAH-sponsored studies.

- AI455055 (2006): Phase 1/2 randomized, multicenter, double-blind study in treatment-naive subjects (24 weeks),
- AI455106 (2006): Phase 4 randomized, multicenter, open-label, prospective, active-controlled, 2-arm study in patients who had experienced virologic failure on a previous d4T-containing regimen (48 weeks),
- AI455110 (2005/2006): Phase 3 active-controlled, multiple-arm, rollover study with subjects who had received d4T ER in Studies AI455096 or AI455099 (204 weeks total for parent study + AI455110),
- AI455131 (DART II) (2006): Phase 3b multicenter, open-label, single-arm, prospective study in treatment-naïve subjects (96 weeks),
- AI455131 (extension) (2008): Phase 3b multicenter, open-label, single-arm, prospective study in treatment-naïve subjects (12-month extension phase),
- AI455135 (ZEST-QD) (2006): Phase 3b open-label, randomized, multicenter study switching subjects with a viral load < 50 copies/mL on a BID or more frequent initial HAART regimen to QD regimen (48 weeks).

The study designs, dosing regimens, and key efficacy data for these 6 studies are summarized in Attachment 8.

In addition, a review of the published literature (January 2005 through June 2010) was conducted using 4 databases (AIDS Clinical Trial Insights, Medline, Derwent Drug Files, and Excerpta Medica). Approximately 1000 key journal articles and key meeting abstracts were retrieved and reviewed by the MAH.

The CHMP agreed with the assessment of the MAH on these data and concluded that, with regards to efficacy and resistance outcomes, these studies did not generate data that needed labelling changes. The efficacy profile of stavudine is well characterized.

2.4.2. Clinical safety

2.4.2.1. Cumulative experience from 24 June 2005 to 31 July 2010

Estimated drug exposure

Zerit has been authorised in the EU since 8 May 1996 and is marketed in 30 Member States and Norway.

Cumulative Exposure

The estimated patient exposure is derived from sales figures received from Intercontinental Marketing Services (IMS) Health data sources and remains an approximation of total quantity of stavudine sold during the period from 24 June 1994 to 31 March 2010, inclusive. Based on the above information, 39,467,023,544 mg were sold during the period referenced. The total number of patients exposed during the period referenced above is estimated to be 1,351,610.

Cumulative Exposure (European Union)

The estimated patient exposure is derived from sales figures received from IMS Health data sources and remains an approximation of total quantity of stavudine sold during the period from 24 June 1994 to 31 March 2010, inclusive. Based on the above information, 11,764,899,718 mg were sold during the period referenced and the total number of patients exposed during the period referenced above is estimated to be 402,907.

Current Marketed Drug Exposure (European Union)

There is no readily available information on the actual number of patients treated with stavudine during the reporting period. However, an estimate of the number of treated patients is derived from sales figures from IMS Health data sources for the period from 01 January 2005 to 31 March 2010, inclusive. Based on the above information, 1,644,269,658 mg were sold during the period referenced above and the total number of patients exposed during the period referenced above is estimated to be 56,211.

The numbers of patients treated with stavudine has declined during the last 5 years (see table 1 below).

Table 1. Global exposure for stavudine during the last 5 years

PSUR Period	Estimated numbers treated
June 2005 to June 2006	65,016
June 2006 to June 2007	42,377
June 2007 to June 2008	27,744
June 2008 to June 2009	18,834
June 2009 to June 2010	9,337

In fulfilment of FUMs #53, the MAH provided data, based on figures from IMS Health, on the estimated number of patients treated at the time of the previous and present 5-year renewal in 10 EU countries, (see table 2 below).

Table 2. Estimated number of patients treated with Zerit in years 2005 and 2009-2010 in 10 EU countries.

	2005	1Q09-1Q2010	Estimated no HIV+ (UNAIDS data 2008)
Spain	7653	2168	140.000 (80 -230.000)
Italy	7637	1346	150.000 (110-210.000)
France	3827	610	140.000 (78-240.000)
Germany	1650	468	53.000 (31-97.000)
UK	1056	163	77.000 (37-160.000)
Belgium	564	103	
NL	350	69	
Austria	211	1[illegible]	
Hungary	31	13	
Sweden	35	5	6200 (3-11.000)
All	23014	4963	

2.4.2.2. Studies during the last 5-year renewal period

A review of 7 MAH-sponsored clinical studies addressing safety and performed during the last 5-year renewal was provided.

- AI455055 (2006) - Phase 1/2 randomized, multicenter, double-blind study in treatment-naive subjects (24 weeks),
- AI455096 (2006) - Phase 4 randomized, multicenter, open-label, prospective, active-controlled, 2-arm study in patients who had experienced virologic failure on a previous stavudine-containing regimen (48 weeks),
- AI455110 (2006) - Phase 3 active-controlled, multiple-arm, rollover study with subjects who had received d4T ER Studies AI455096 or AI455099 (132 weeks),
- AI455120 (2005) - Phase 3b uncontrolled, observational study designed to provide long-term safety monitoring of infants who were born during Study AI455094 (5-year analysis),
- AI455131 (2006) - Phase 3b multicenter, open-label, single-arm, prospective study in treatment-naïve subjects (96 weeks),
- AI455131 (extension) (2008) - Phase 3b multicenter, open-label, single-arm, prospective study in treatment-naïve subjects (12-month extension phase),

- AI455135 (ZEST-QD) (2006) - Phase 3b open-label, randomized, multicenter study switching subjects with a viral load < 50 copies/mL on a BID or more frequent initial HAART regimen to QD regimen (48 weeks).

No new safety information of relevance was found in these studies as the safety characteristics are well known for stavudine.

Study AI455-120 is ongoing. It consists of an Observational Protocol for the study AI455094 Late Outcomes. The primary objective was to describe and assess the long-term health and development of children who received ART *in-utero* and during the newborn period for prophylaxis of mother to child transmission (MTCT) of HIV during the conduct of the study AI455-094. One hundred forty seven (147) patients were enrolled, 147 patients were randomized. The second 5 years interim study report was submitted by the MAH in January 2011 and will be assessed as part of FU2 44.1 which started on 13th February 2011.

A number of non-sponsored investigator-initiated studies were also published during this time frame. One of those studies is of particular interest with regards the safety profile (i.e. lipoatrophy) of stavudine in comparison to that of other NRTI backbones (Haubrich, AIDS 2009). This study is discussed in a subsection concerning lipoatrophy in Section 2.4.2.3.

2.4.2.3. Report of post marketing experience from 24 June 2005 to 31 July 2010

Table 3 summarise the post marketing experience submission since the last renewal application. PSUR data from 24 June 2005 to 23 June 2008 was assessed as part of FUM 50.

Table 3. Periodic Safety Update Report (PSUR) submissions

PSUR Sequence	Period Covered
12th PSUR submission	24 June 2005 to 23 June 2006 24 June 2006 to 23 June 2007 24 June 2007 to 23 June 2008
PSUR submission within this renewal application	24 June 2008 to 23 June 2009
PSUR submission within this renewal application	24 June 2009 to 23 June 2010
PSUR Addendum Report within this renewal application	24 June 2010 to 31 July 2010

Hence, the MAH submitted within the renewal dossier:

- PSUR covering from 24 June 2008 to 23 June 2009
- PSUR covering from 24 June 2009 to 23 June 2010
- PSUR Addendum Report covering from 24 June 2010 to 31 July 2010
- Summary bridging report covering from 24 June 2005 through 23 June 2010.

The complete assessment of the PSURs covering from 24 June 2008 to 23 June 2009 and the PSUR covering from 24 June 2009 to 23 June 2010 are attached in Attachments 6 and 7. A summary of the key elements of these assessments is provided below.

Analyze of PSUR report covering the period from 24 June 2008 to 23 June 2009
Presentation of Individual Case Histories / Adverse Events

During the reporting period from 24 June 2008 through 23 June 2009, a total of 204 AEs reports were received and/or validated, which included stavudine oral formulation as a suspect or interacting drug, and met the qualification for inclusion in the PSUR. Forty-six (46) were spontaneously reported from worldwide sources, 87 were derived from the published scientific literature, and 71 were received from clinical trials. One hundred seventy one (171) of the 204 events qualified for classification as serious and 33 were non-serious. Additionally, there were 8 non-healthcare professional confirmed cases, of which 4 were serious. A fatal outcome was reported in 25 of the total of 204 cases.

Metabolism and nutrition disorders

There were a total of 31 events, including 5 serious, unlisted (dehydration, hyperlipidemia, and metabolic acidosis, mitochondrial toxicity x 2), 13 serious, listed (anorexia, diabetes mellitus x 2, hyperlactemia, lactic acidosis x 9), and 13 nonserious events. Cumulatively, there have been a total of 43 events of metabolic acidosis and 37 of mitochondrial toxicity.

Death

The reporting rate of fatal cases during this PSUR period is comparable with previous PSUR periods. Of the 25 cases with a fatal outcome, 18 were assessed as not related to stavudine. Of the 25 reports, 5 reports did not have the cause of death provided. In two of the 25 reports, the death was due to an event that is adequately described in the product label (lactic acidosis, metabolic acidosis).

Given the nature and progression of HIV disease, fatal outcomes are expected in this population of severely immunosuppressed patients. Confounding factors such as opportunistic infections, cirrhosis, malignancies and multiple drug regimens leading to metabolic, cardiac, and hepatic disorders were reported in the majority of reports as either a cause of death or a concurrent event.

Special patient groups

Paediatric use

During the reporting period, among files for which the age of the patient was reported, there were a total of 29 healthcare professional confirmed reports (27 initial and 2 follow-up) of AEs occurring in patients 17 years of age or younger. Of these reports, 13 were spontaneous reports, 5 were derived from published literature and 11 were study reports. Furthermore, 15 reports were classified as serious.

The reported events experienced in the pediatric population were Blood bilirubin increased, Blood bilirubin unconjugated increased, and Lipodystrophy acquired.

Elderly use

During the reporting period, among files for which the age of the patient was reported, there were 2 healthcare professional confirmed reports (1 initial and 1 follow-up) of AEs occurring in patients 65 years of age or older. Of these reports, none were spontaneous reports, 2 were derived from published literature and none were study reports. Furthermore, both the reports were classified as serious.

The reported events experienced in the elderly population were abnormal dreams, malignant melanoma, metastases to lymph nodes, metastases to skin, and neoplasm malignant.

Renal impairment

There were 4 serious cases reported that included patients with a history of renal impairment. Of these 4 reports, 1 was spontaneous, 3 were reported in the literature and none were study reports. The reported events in this population were ascites, fatigue, hepatitis, escherichia urinary tract infection, weight decreased, lactic acidosis, neuropathy peripheral, polyneuropathy, and abnormal dreams.

Liver impairment

There were 7 serious cases reported that included patients with a history of liver impairment. Of these 7 reports, 3 were spontaneous, 3 were reported in the literature and 1 was a study report. The reported events in this population were Myocardial infarction, Ascites, Diarrhoea, Haematemesis, Pancreatitis acute, Varices oesophageal, Fatigue, Pyrexia, Virologic failure, Hepatic cirrhosis, Hepatic failure, Hepatic steatosis, Escherichia urinary tract infection, Blood ALP increased, Blood amylase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Transaminases increased, Weight decreased, Diabetes mellitus, Hyperlactacidaemia, Hyperlipidaemia, Lactic acidosis, Neuropathy peripheral, Renal failure acute, Cough, Lipodystrophy acquired, and Rash maculopapular.

The CHMP concluded that the events reported in these special populations are in line with the known safety profile of the product.

Pregnancy and lactation

A search of the safety database for the period covered by this report identified a total of 265 reports (243 initial and 22 follow-up) of stavudine exposure during pregnancy. Of these, 7 were spontaneous reports, 1 was derived from published literature and 257 were study reports. Furthermore, 28 reports were classified as serious. There were 3 reports that were not confirmed by a healthcare professional.

The outcome for these pregnancy cases, when reported, included 232 live births, normal (179 live births, 53 normal newborns), 1 premature baby, 1 intra-uterine death, 5 spontaneous abortions, 14 abortions induced, 6 congenital abnormalities and 1 death neonatal.

A cumulative search of the safety database to 23 June 2009 inclusive identified 1,929 reports of stavudine exposure during pregnancy. Of these, 298 were spontaneous, 30 were derived from published literature, and 1601 were study reports. Furthermore, 606 reports were classified as serious. There were 16 reports that were not confirmed by a healthcare professional.

There were no cases of infant exposure to stavudine via breast milk during this reporting period.

The CHMP concluded that, relative to prior reporting periods, there were no significant differences involving the clinical outcomes following stavudine exposure during pregnancy. It is difficult to determine a causal relationship of the congenital abnormalities, spontaneous abortions, premature birth, neonatal disorders and fetal disorders to stavudine alone since the mothers were receiving multiple ART medications. No AEs described in this reporting period were more frequent or severe than those expected during pregnancy with exposure to stavudine in HIV-infected patients. These data are consistent with the known safety profile for stavudine.

Conclusions from the CHMP on the PSUR report covering the period from 24 June 2008 to 23 June 2009

The data presented in this PSUR reveal no previously unrecognized AEs or new safety concerns. The AEs reported during this period are adequately reflected in the SPC. However, it was noted that the PSUR does reveal the persistent safety concerns of those severe AEs of lactic acidosis, lipoatrophy and polyneuropathy which are caused by mitochondrial toxicity.

Analyze of PSUR report covering the period from 24 June 2009 to 23 June 2010
Presentation of Individual Case Histories / Adverse Events

During the reporting period from 24 June 2009 through 23 June 2010, a total of 362 AE reports were received and/or validated, which included stavudine oral formulation as a suspect or interacting drug.

Two hundred and fifty eight (258) were spontaneously reported from worldwide sources, 74 were derived from the published scientific literature, and 30 were received from clinical trials. One hunder and eleven (111) of the 362 events qualified for classification as serious and 251 were nonserious. Additionally, there were 6 non-healthcare professional confirmed cases, of which 4 were serious. A fatal outcome was reported in 12 of the total of 362 cases.

Metabolism and nutrition disorders

There were a total of 25 events, including serious events of diabetes (3), dyslipidemia, hypercalcemia, hyperlactemia, hyperlipidemia (3), hypertriglyceridemia (3), lactic acidosis (3), mitochondrial cytopathy, and mitochondrial toxicity (2). Cumulatively, there have been 18 events of mitochondrial cytopathy and 39 of mitochondrial toxicity.

Table 4 presents a stavudine 5-year cumulative table of AEs for the PT, Lactic acidosis. The search criteria used to obtain the cumulative data are as follows:

• All health professional confirmed spontaneous reports (serious and non-serious),

• All literature reports (serious and non-serious),

• All serious phase 1 through 4 clinical trial reports (causally related).

Table 4. stavudine 5-year cumulative table of AEs for the PT, Lactic acidosis

Stavudine Annual Cumulative Data for PT Lactic Acidosis (5 years)			
PSUR annual period	Patient Exposure[a]	Lactic Acidosis	Rates of Reports/Exposure (%)[b]
24 June 2005 to 23 June 2006	65,016	29	0.045
24 June 2006 to 23 June 2007	42,377	25	0.059
24 June 2007 to 23 June 2008	27,744	17	0.061
24 June 2008 to 23 June 2009	18,834	6	0.032
24 June 2009 to 23 June 2010	9,337	3	0.032

[a] Estimated patient exposure = total mg sold / total mg per patient, assuming patient receives 40 mg twice daily continuously for 1 year (365 days). The patient received a total dose of 29,200 mg.

[b] Number of reports divided by the estimated number of patients exposed multiplied by 100 equals the percent of patient exposure.

Death

A total of 12 healthcare professional confirmed cases were reported with a fatal outcome. Of these cases, 7 were derived from the scientific literature, 3 were clinical trial cases, and 2 were spontaneous cases. The cases described patients who ranged in age from 17 to 54 years (mean = 40.7 years N = 11). Of the 12 cases with a fatal outcome, 1 was assessed as not related to stavudine. In 4 of the 12 cases, the death was due to an event that is adequately described in the product label or was due to progression of underlying disease. The most frequently reported causes of death were Immune reconstitution syndrome (2) and Metabolic acidosis (2). Additionally, there was 1 case with a fatal outcome in which the cause of death was unknown or not reported.

Special patient groups

Paediatric use

During the reporting period, among files for which the age of the patient was reported, there were a total of 21 healthcare professional confirmed cases of AEs occurring in patients 17 years of age or younger. The most frequently reported events experienced in the pediatric population were Blood bilirubin increased (9), Blood bilirubin unconjugated increased (8), and Delirium (3).

Elderly use

During the reporting period, among files for which the age of the patient was reported, there was 1 healthcare professional confirmed case of AEs occurring in a patient 65 years of age or older.

Renal impairment

There were 2 serious cases reported that included patients with a history of renal impairment. The reported events in this population were Angina unstable, Drug interaction, Serotonin syndrome, and Delirium.

Liver impairment

There were 6 serious cases reported that included patients with a history of liver impairment. The most frequently reported event in this population was hepatic cirrhosis.

Pregnancy and lactation

A search of the safety database for the period covered by this report identified a total of 273 cases (264 initial and 9 follow-up) of stavudine exposure during pregnancy. Of these, 243 were spontaneous cases, 2 were derived from the scientific literature, and 28 were clinical trial cases. Furthermore, 10 cases were classified as serious. Approximately 240 of the 273 pregnancy cases were received from a physician in South Africa via Merck.

The outcome for these pregnancy cases, when reported, included 203 live birth, normal; 3 live birth, abnormal (including pre-term, term, post-term birth, small for gestational age infants intrauterine growth retardation, drug withdrawal syndrome in the neonate, malformations, morbidity); 6 termination of pregnancy, and 5 foetal abnormalities. There were no foetal death cases (ectopic, miscarriage, and stillbirth).

A cumulative search of the safety database to 23 June 2010, inclusive, identified 2,189 cases of stavudine exposure during pregnancy. Of these, 536 were spontaneous, 32 were derived from the scientific literature, and 1,621 were clinical trial cases.

Furthermore, 610 cases were classified as serious. There were 16 cases that were not confirmed by a healthcare professional.

There were no cases of infant exposure to stavudine via breast milk during this reporting period.

The CHMP concluded that, relative to prior reporting periods, there were no significant differences involving the clinical outcomes following stavudine exposure during pregnancy. It is difficult to determine a causal relationship of the congenital abnormalities, spontaneous abortions, premature birth, neonatal disorders and fetal disorders to stavudine alone since the mothers were receiving multiple ART medications. No AEs described in this reporting period were more frequent or severe than those expected during pregnancy with exposure to stavudine in HIV-infected patients. These data are consistent with the known safety profile for stavudine.

Long-term treatment

While the short-term tolerability of stavudine is good, longer-term therapy has been associated with several potentially severe side effects, including lactic acidosis (occurring typically after some months), lipoatrophy (typically starting to occur after first year), and polyneuropathy (occurring typically after some months) for which the potential underlying mechanism is mitochondrial toxicity.

Conclusions from the CHMP on the PSUR report covering the period from 24 June 2009 to 23 June 2010

The data presented in this PSUR reveal no previously unrecognized AEs or new safety concerns. However, the PSUR does reveal the persistent safety concerns of those severe AEs of lactic acidosis, lipoatrophy and polyneuropathy which are caused by mitochondrial toxicity.

Analyze of PSUR addendum report covering the period from 24 June 2010 to 31 July 2010

During this reporting period, 23 initial healthcare professional confirmed AEs reports were received and/or validated that included stavudine as a suspect or interacting drug. Of these, 17 were spontaneously reported from worldwide sources, 4 were derived from the published scientific literature and 2 were received from clinical trials. Furthermore, 6 of the 23 reports qualified for classification as serious: 3 literature reports, 2 clinical trial reports and 1 spontaneous report.

Overall, there were 14 reports that involved drug exposure during pregnancy and 1 report that described suspected drug interaction. There were no reports of overdose, potential drug abuse and medication error/maladministration. A fatal outcome was reported in 2 of the total 23 reports.

During the period of this update, no previously unrecognized AEs with stavudine have been identified.

Conclusions from the CHMP on the PSUR addendum report covering the period from 24 June 2010 to 31 July 2010

During this reporting period no new safety concerns were identified that are not consistent with the known safety profile of the product.

Cumulative review of the renewal 5-year period from 24 June 2005 to 31 July 2010

Spontaneous reports, literature, and clinical study reports associated with the use of stavudine were derived from a comprehensive search of the BMS Corporate Adverse Event Reporting and Evaluation System (CARES) post-marketing worldwide safety database.

A total of 1,345 healthcare professional confirmed adverse event (AE) reports (1,189 initial and 156 follow-up) that included stavudine formulations as the suspect or interacting drug were validated.

- 531 spontaneously reported,
- 424 derived from the publications,
- 390 received from clinical trials.

Nine hundred eighty four (984) were qualified as serious (207 spontaneous, 387 scientific literature, and 390 from clinical trials). A fatal outcome was reported in 150 of the 1,345 reports. These reports have already been handled within the periodic safety updates (PSURs).

Events reviewed during specific PSUR reporting periods due to CHMP's requests

In variation IA/75, adopted by the CHMP on 22nd July 2010, sections 4.4 and 4.8 of the SmPC were updated to include 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 acidosis has been moved from unknown to uncommon in the tabulated Summary of the Adverse Drug Reactions in the section 4.8 of the SmPC.

As part of this variation, the CHMP acknowledged that the extensive mitochondrial toxicity of stavudine and the consequences of such toxicity have been already known. However, as a number of studies assessing various regimens and including objective measurements of body fat (DEXA-scanning) have been published recently, the frequency and the severity of these adverse reactions became clearer:

There is enough evidence to reconsider the whole "lipodystrophy syndrome" as a consequence of mitochondrial toxicity. Abdominal fat accumulation does no longer seem to be an adverse event of

antiretrovirals, but rather the visual effect of central weight gain in combination with the loss of subcutaneous fat (in practice thymidine analogues). The initially optimistic switch studies, which reported improvements of subcutaneous fat when stavudine was replaced by abacavir/tenofovir, has later in practice shown that lipoatrophy is quite irreversible in many patients with extensive lipoatrophy, and for other patients improvements have been quite modest.

In addition, stavudine also carries a risk for lactic acidosis in the order of 1% of those treated for a few months or longer and polyneuropathy is developed in around 1/5 patients.

Hence, in conclusion of variation II/75, the CHMP requested the MAH to submit the data listed as part of FUM 53 in the present renewal application as they are useful for a re-eavluation of the benefit/risk balance of this product.

Lipoatrophy/body fat changes

Reported number of events during the renewal period

The number of events reported is shown in the table 5.

Table 5. Reported number of lipoatrophy events during the renewal period

	PSUR Period				
MedDRA Preferred Term	**24-Jun-2005 to 23-Jun-2006**	**24-Jun-2006 to 23-Jun-2007**	**24-Jun-2007 to 23-Jun-2008**	**24-Jun-2008 to 23-Jun-2009**	**24-Jun-2009 to 23-Jun-2010**
	No. of Reports (% Rate of Reports) [a]				
Lipodystrophy Acquired	20	14	10	27	8
Lipoatrophy	22	13	6	1	2
Lipohypertrophy and Facial Wasting	5	4	1	1	2

Lipoatrophy was shown to occur within the first years of treatment in the majority of patients treated with stavudine (some 40% within two years of treatment in clinical trials). As the exposure to stavudine has decreased over the recent years, the reports concerning this adverse reaction have also declined over time.

Clinical studies and lipoatrophy during the renewal period

Table 6 summarizes such data for studies (all in treatment naïve patients) including DEXA-scanning and treatment with stavudine in at least one treatment arm.

Table 6. Relevant studies with DEXA-scanning (body fat changes).

Study	Treatment	Fat changes by DEXA at week 96
ACTG5142 (Haubrich, 2009)	1) lopinavir/r + 2 NRTI vs 2) efavirenz + 2 NRTI vs 3) lopinavir/r + efavirenz *NRTI choice (arms 1 and 2):* stavudine/3TC *or* zidovudine/3TC o*r* tenofovir/3TC	Lipoatrophy (i.e. loosing > 20% limb fat) - stavudine: 42% of patients - zidovudine: 27% - tenofovir: 9% Trunk (mean) + 2.2 kg regardless of treatment arm and NRTI selection.
ABCDE (Podzamczer, 2007)	stavudine/3TC *vs* abacavir/3TC + efavirenz	Clinical signs of lipoatrophy at week 96 stavudine-arm: 38% of patients abacavir-arm: 5% of patients stavudine: limbs (-1.6 kg); trunk (+ 1.0 kg) abacavir: limbs (+ 0.9 kg); trunk (+ 1.2 kg)
Gilead 903 (Gallant, 2004)	stavudine *vs* tenofovir + 3TC/efavirenz	Limbs: stavudine: 5.0 kg fat (absolue)[#] tenofovir: 7.0 kg fat (absolue)[#] [#] *(DEXA not performed at BL)* Trunk: Not mentioned in publication
NCT00084253 (McComsey 2009)	atv/r (300/100 qd) *vs* atv (400 qd) + stavudine	Limbs: atv/r: -9% atv: -17% Trunk: atv/r: +16% atv: +14%

The study published by Haubrich et al, AIDS 2009, suggested for the first time that the development of lipoatrophy is quicker - and potentially more severe - with stavudine than with zidovudine.

The CHMP also noted that the subcutaneous fat loss (by DEXA measured on extremities) was universal in patients treated with stavudine. However, this event seems to be scarce in those treated with recommended first line NRTIs (e.g. abacavir, tenofovir), as well as in those treated with non NRTI regimens.

Lactic acidosis

Reported number of events during the renewal period

Eighty two (82) cases (all serious) of lactic acidosis were reported (17 spontaneous, 20 from clinical trials, and 45 from published literature). Two reports derived from the scientific literature were composite cases, and were not included in the total count analysis of the individual cases from the CARES safety database. Of the remaining 80 cases, the outcome for the events of lactic acidosis was recovered/resolved in 22, recovering/resolving in 4, not recovered/not resolved in 3, and unknown/not reported in 22.

Overall, there were 29 reports with a fatal outcome, of which 20 reported lactic acidosis as the cause of death.

Clinical studies and lactic acidosis during the renewal period

The MAH provided a tabulated summary of recent studies concerning stavudine and lactic acidosis from worldwide literature (see Table 7). These data mainly concern low income regions. For example similar figures are presented from two different studies in Botswana and South Africa, with an incidence of lactic acidosis in around 1% of patients treated with stavudine (Wester 2007, Stead 2008).

Table 7. Summary of Studies with Data on Lactic Acidosis from the Worldwide Literature.

Author	Study Design/Treatment/Patient Population
Lactic Acidosis International Study Group[i] (2007)	Retrospective, multicenter, case-control study in patients with HIV-1 infection. Cases = 110 (49 with lactic acidosis) and 220 controls.
Results: In a multivariate model, hyperlactatemia was associated with exposure to ddI in every category of exposure duration, but was most strongly associated with exposure < 12 months. In a separate model, apart from exposure to d4T, ddI, or even more strongly both drugs, age > 40 years, female gender, and advanced immunosuppression were independent associations.	
Wester et al (Tshepo study) (2007)	Randomized, open-label, factorial design study in 650 patients with HIV infection followed for 3 years. ART options included ZDV/3TC/NVP, ZDV/3TC/EFV, ZDV/ddI/NVP, ZDV/ddI/EFV, d4T/3TC/NVP, or d4T/3TC/EFV.
Results: Fifteen patients (2%) developed moderate to severe symptomatic hyperlactatemia, with 7 patients (1%), all female, diagnosed with lactic acidosis. Four of these 7 patients died of lactic acidosis and/or hemorrhagic pancreatitis. Of these 15 patients, ART was d4T/3TC/EFV (6 patients), d4T/3TC/NVP (3 patients), CBV/EFV and d4T/ddI/NFV (2 patients each), and ZDV/ddI/EFV and d4T/ddI/NVP (1 patient each). Female gender and BMI > 25 were predictive for the development of moderate to severe symptomatic hyperlactatemia or lactic acidosis (p=0.001), but exposure to d4T and/or ddI for ≥ 6 months was not predictive.	
Stead et al (2008)	Retrospective case review study of 75 patients with HIV infection on ART with severe symptomatic hyperlactatemia
Results: Of the 75 patients with severe symptomatic hyperlactatemia, 71 were female, and all had been on d4T and on ART for a median of 10 months. The referral rate for severe symptomatic hyperlactatemia was 17.5 cases per 1,000 patient-years. In 53 patients (71%), lactic acidosis was confirmed, with a referral rate of 12.3 cases per 1,000 patient-years. Twelve patients (16%) died during acute admission (< 30 days). Standard bicarbonate < 15 mmol/L and pH < 7.2 were the only factors associated with acute mortality. Thirty less severe cases were rechallenged with ZDV without recurrence of severe symptomatic hyperlactatemia.	
3TC = lamivudine, ART = antiretroviral therapy, BMI = body mass index, CBV = carbovir, d4T = stavudine, ddI = didanosine, EFV = efavirenz, HIV = human immunodeficiency virus, HIV-1 = human immunodeficiency virus-type 1, NVP = nevirapine, and ZDV = zidovudine	

The CHMP noted that lactic acidosis was also reported in around 1-2% of patients treated with stavudine in larger cohorts in low income regions (e.g. reviewed by Makinson Expert Opinion Drug Safety 2010), and in a similar number also in a US cohort (Lonergan, CID 2000).

In addition, some randomized controlled trials reported lactic acidosis/symptomatic hyperlactemia in patients treated with stavudine, but not in those treated with abacavir or tenofovir (see table 8).

Table 8. Report of symptomatic hyperlactatemia/lactic acidosis

Reference	Report of symptomatic hyperlactatemia/lactic acidosis
Gilead 903-study (Gallant, 2004)	stavudine-arm 3/301; tenofovir-arm 0/299
ABCDE-study (Podzamczer, 2007)	stavudine-arm 4/122; abacavir-arm 0/115

In summary, from various settings, including patients in randomized studies, figures are fairly similar with a risk developing lactic acidosis of around 1% of those treated with stavudine. In contrast, this risk is exceedingly uncommon during treatment with other NRTIs.

Peripheral neuropathy

Reported number of events during the renewal period

There were 54 cases that contained the terms of Guillain-Barresyndrome (2), polyneuropathy (15), neuropathy peripheral (35), peripheral sensorimotor neuropathy (1), and peripheral sensory neuropathy (1). Of these cases, 12 were from clinical trials, 20 were spontaneous cases, and 22 were from published literature. Forty-nine (49) cases were serious.

Clinical studies and peripheral neuropathy

Table 9 summarizes the data from the more recent studies regarding peripheral neuropathy and stavudine treatment.

Table 9. Summary of Studies with Data on Peripheral Neuropathy from the Worldwide Literature

Author	Study Design/Treatment/Patient Population
Hulgan et al ACTG 384 study (2005)	Retrospective, 3-year case-control study of 509 patients who had participated in ACTG 384 study and contributed DNA to the ACTG Human DNA Repository. ACTG 384 was a randomized, multicenter study in patients who had received < 7 days of prior ART. They were randomized to receive 3- or 4-drug therapy with ddI+d4T or ZDV+3TC in combination with EFV or NFV or EFV+NFV.
Results: Peripheral neuropathy of any grade was reported in 147 patients (29%). Of these patients, 108 (73%) had been randomized to receive ddI+d4T and 39 (27%) had been randomized to receive ZDV+3TC (p<0.001). These patients had lower baseline plasma HIV-1 RNA concentrations (p=0.004), and were older at study entry (p=0.0001) than patients who did not develop peripheral neuropathy. Among White patients, those who developed peripheral neuropathy were older (p=0.01) and more likely to have been randomized to d4T+ddI (p=0.007) than White patients who did not develop peripheral neuropathy. Among 137 White patients randomized to receive ddI+d4T, 21% of those who developed peripheral neuropathy belonged to mitochondrial haplogroup T compared to controls (5%) (odds ratio = 5.4; p=0.009).	
Cherry et al Nerve Project (2006)	Two-center study of 147 subjects with HIV exposed to potentially neurotoxic NRTIs. Twenty-six patients had received zalcitabine, 111 patients had received d4T, and 87 patients had received ddI.
Results: After adjusting for site, age, and CD4 cell count, exposure to d4T or ddI was associated with a significantly increased likelihood of symptomatic sensory neuropathies (odds ratio = 3.21; 95% CI: 1.56, 6.60 for ddT and odds ratio = 7.66; 95% CI: 2.89, 20.33 for d4T).	
Skopelitis et al (2006)	Single-center study of 100 patients with HIV exposed to potentially neurotoxic NRTIs and followed up in the outpatient clinic. Group 1 had prior or current exposure to at least 2 of the major neurotoxic ARVs (ddI, d4T, or zalcitabine) at a time (15 patients), Group 2 had exposure to 1 of the 3 drugs at a time

Author	Study Design/Treatment/Patient Population
	(30 patients), and Group 3 had no exposure to these 3 drugs (48 patients).
Results: Thirty-six percent of patients developed distal sensory polyneuropathy, although it was subclinical in 2/3 of cases. Distal sensory polyneuropathy developed in 11/15 patients (73%) in Group 1, 10/30 patients (30%) in Group 2, and 15/48 patients (31%) in Group 3, and the differences between groups were significant (p=0.0189). Age, severe prior immunosuppression, and the combined use of zalcitabine, d4T, and ddI are important risk factors for the development of distal sensory polyneuropathy.	
Konchalard and Wangphonpattanasiri[ii] (2007)	Single-center study of 34 patients with HIV; 24 had received ART: d4T+3TC+EFV (14 patients), AZT+3TC+NVP (4 patients), AZT+3TC+EFV and d4T+3TC+EFV (2 patients each), and 3TC+EFV+ddI and AZT+3TC+IDV+RTV (1 patient each).
Results: Seventeen of 34 patients (50%) developed HIV-related neuropathy. Patients with HIV-related neuropathy had significantly lower CD4 cell counts than patients without HIV-related neuropathy (p<0.05). The only correlation between ART and the development of HIV-related neuropathy was a trend for d4T use (p=0.063).	
Smyth et al (2007)	Cross-sectional comparative study using convenience sampling of patients with HIV. The cohorts were 1993 (94 patients), 2001 (141 patients), and 2006 (100 patients). Zalcitabine use: 39 in 1993 and 32 in 2001 and 2006; ddI use: 54 in 1993, 56 in 2001, and 42 in 2006; and d4T use: 0 in 1993, 76 in 2001, and 58 in 2006.
Results: The prevalence of HIV-associated sensory neuropathy was 42% in 2006, which was unchanged since 2001 (44%) despite a significant reduction in the use of zalcitabine, ddI, and d4T, and significantly higher than in 1993 (13%) (p<0.0001). the only independent associations with HIV-associated sensory neuropathy were increasing age and a history of exposure to either d4T or IDV.	
Affandi et al (2008)	Single-center study of 96 patients who had ever been treated with d4T.
Results: The prevalence of sensory neuropathy (signs and symptoms) was 34%. Multivariate analysis showed that neuropathy following d4T exposure was associated with increasing age, increasing height, and the presence of the TNFA-1031*2 allele (p=0.0009). The data suggest that a simple algorithm based on patient age, height, and TNF genotype could be used to predict a patient's risk of symptomatic neuropathy prior to prescription of d4T.	
Hung et al (2008)	Prospective single-center study of the rates of worsening neuropathic symptoms and signs in patients with HIV on stable ARV regimens containing dideoxynucleosides (252 patients) or not (250 patients).
Results: The hazard ratio for worsening neuropathy signs was not significantly different for patients taking non-dideoxynucleoside drugs compared to patients taking dideoxynucleoside drugs (hazard ratio = 0.94; 95% CI: 0.84-1.07; p=0.64). Similarly, there was no increase in risk for worsening neuropathy symptoms (hazard ratio = 0.99; 95% CI: 0.88-1.14; p=0.93).	
Cherry et al (2009)	Cross-sectional neuropathy screening at 3 centers in 2006 in 294 patients with HIV and treated with d4T.
Results: Ninety-four patients (32%) met the definition of neuropathy. In addition to treatment exposures, increasing age (p=0.002) and height (p=0.001) were independently associated with neuropathy. Among 181 patients who were asymptomatic before d4T exposure, the risk of neuropathy following d4T was 20% in younger, shorter patients compared with 66% in older, taller patients.	
3TC = lamivudine, ART = antiretroviral therapy, ARV = antiretroviral, AZT or ZDV = zidovudine, CI = confidence interval, d4T = stavudine, ddI = didanosine, DNA = deoxyribonucleic acid, EFV = efavirenz, HIV = human immunodeficiency virus, HIV-1 = human immunodeficiency virus-type 1, IDV = indinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, RNA = ribonucleic acid, and RTV = ritonavir	

In summary these studies all show that stavudine-associated peripheral neuropathy is common and troublesome especially in those countries where the use of stavudine is the most common (low income regions); here patients to a large extent also have other risk factors for neuropathy, such as malnutrition and tuberculosis treatment including isoniazide. The frequency of neuropathy in the Gilead 903 study (stavudine vs tenofovir, both in combination with lamivudine and efavirenz) was higher with stavudine than with tenofovir (10% vs 3%).

2.4.2.4. Conclusion on Safety

The main safety issue related to the use of stavudine is the mitochondrial toxicity. Lactic acidosis, with a case fatality rate of 20-60%, affects around 1% of those treated (according to cohort studies). The symptoms are non-specific, and there is no measure/tool that can be used to predict those patients who will be affected by this adverse event. Lipoatrophy, the loss of subcutaneous fat tissue, is seen in almost half the patients already after some 2-3 years of treatment, and in the longer term probably affects the vast majority of those treated with stavudine. The reversibility of this adverse event is slow and for many patients only partial. Lipoatrophy is regarded as a most stigmatizing adverse event by the patients affected. In addition, neuropathy is commonly seen during treatment with stavudine (10-20% of treated patients) and has a slow reversibility upon stopping the treatment. These risks are well characterised in the current SmPC for stavudine.

Since the last renewal for stavudine in 2006, the standard of assessment of HIV medicinal products has evolved, notably due to the approval of a number of new medicines in the European Union for the treatment of HIV (new therapeutic classes e.g. CCR5 antagonists, integrase inhibitors, new molecules in an existing class e.g. protease inhibitors). The approval of these medicines introduced a significant progress in the treatment of HIV due to their therapeutic efficacy and safety profile (notably regarding mitochondrial toxicity).

Despite the fact that the safety profile for stavudine is well described in the SmPC, the CHMP was concerned that AEs of mitochondrial toxicity are still being reported in the recent years.

A HIV / Anti Viral Scientific Advisory Group (HIV / AV SAG) was convened at the CHMP requestThe SAG was asked to discuss the role of stavudine in the treatment of HIV infected patients in the European Union and were asked to determine patients groups for which stavudine, in the view of its toxicity profile, would be considered as an appropriate treatment.

By consensus, the SAG concluded that there is still a role for stavudine in the treatment of HIV-infected patients in the European Union. However, the SAG could not precisely identify the patients population(s) for whom this treatment would be beneficial. It was foreseen that the current use of stavudine in the European Union was essentially historical - i.e. patients treated with this medicine for a long period of time – and it was acknowledged that this use was gradually decreasing. In conclusion, the SAG agreed that only a very limited patients' population would benefit from stavudine treatment in the European Union among which paediatric patients and HIV-2 patients.

Given that the toxicity of stavudine appears with its long term use, it was suggested by the SAG that this medicinal product should be restricted to short duration of treatment where possible. As a consequence, the SAG suggested that the prescribers should consider switching patients who have been treated for a long period with stavudine to other treatments with less risk of mitochondrial toxicity.

Taking into account the data provided as part of this renewal application, the recommendations of the HIV / Anti Viral Scientific Advisory Group (HIV / AV SAG) and the current standard of assessment, the CHMP considered the safety profile of stavudine, especially with regards to the mitochondrial toxicity, justify a restriction of indication. As a consequence, the CHMP concludes that the treatment with stavudine should be restricted to cases where 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 by the CHMP to the shortest time possible. The CHMP furthermore concluded that the treatment with stavudine should be followed by a switch to an alternative

appropriate therapy whenever possible and the patients continuing treatment with stavudine should be assessed frequently and switched to an alternative appropriate therapy whenever possible.

The Product Information has been updated accordingly (refer to section 2.5)

The MAH has agreed with the CHMP request to inform the stakeholders by sending a 'Dear Health Care Professional Letter' within 4 weeks from the adoption of the opinion. This letter will be addressed to the prescribers, the patients' organisations and the patients associations and will inform them of this restriction of indication.

The MAH was requested to submit a Risk Management Plan (RMP) for stavudine as this document was not included in this Marketing Authorisation approved in 1996. (See Annex II.B of the product information)

In addition, the MAH agreed with the CHMP to perform a Drug Utilisation Study (DUS) in order to gather information on the use of Stavudine in the European Union, notably that the prescriptions of stavudine are in line with the restricted indication The protocol of the study will be agreed by the CHMP and the results of the study, together with a comparison of the number of patients treated in the EU between 1Q 2011-1Q2012 and 1Q2010-1Q2011 should be provided by the MAH within 2Q2012. (See Section 2.6 Follow Up Measures).

Finally, the CHMP decided to increase the PSUR submission schedule from a 3 years submission schedule to a 2 years submission schedule. (See Annex II.B of the product information and letter of Undertaking)

2.5. Product information

2.5.1. Summary of product characteristics, labelling and package leaflet

The MAH proposed changes to the Product Information (PI), which were reviewed during the assessment of this renewal application.

During the procedure, the CHMP requested and endorsed the following additional amendments to the Product Information (see text in bold):

Powder for Oral Solution

4.1 Therapeutic Indication:

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected **adult patients and paediatric patients (from birth) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to shortest time possible. (See section 4.2)**

4.2 Posology and method of administration

For patients starting therapy with Zerit, the duration should be limited to shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible. (See section 4.4)

Hard Capsules

4.1 Therapeutic Indication:

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected **adult patients and paediatric patients (over the age of 3 months) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to shortest time possible. (See section 4.2)**

4.2 Posology and method of administration

For patients starting therapy with Zerit, the duration should be limited to shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible. (See section 4.4)

Changes were also proposed by the MAH to the PI (Annex I, IIB, IIIA and IIIB) to bring it in line with the current Agency/QRD template and the SmPC guideline. These changes have been reviewed by QRD and approved by the CHMP.

2.5.2. General conditions for the marketing authorisation

Annex II.B - Conditions:

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan of a Risk Management Plan (RMP) to be submitted within one month from the Commission decision in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSUR

The PSUR will be submitted on a two years basis until otherwise agreed by the CHMP.

Attachment 4 of this Assessment Report includes the SmPC, Annex II, Labelling and PL where all adopted changes are annotated.

2.5.3. Changes to annex A

No changes to the Annex A as part of this renewal procedure.

2.6. Conclusions on benefit risk balance of the product

The efficacy of stavudine as part of a first-line regimen has been established in various randomized controlled trials. No new data was generated with regards to efficacy and resistance outcomes during the renewal period.

The main safety issue related to the use of stavudine is the mitochondrial toxicity. Lactic acidosis, with a case fatality rate of 20-60%, affects around 1% of those treated (according to cohort studies). The symptoms are non-specific, and there is no measure/tool that can be used to predict those patients who will be affected by this adverse event. Lipoatrophy, the loss of subcutaneous fat tissue, is seen in almost half the patients already after some 2-3 years of treatment, and in the longer term probably affects the vast majority of those treated with stavudine. The reversibility of this adverse event is slow and for many patients only partial. Lipoatrophy is regarded as a most stigmatizing adverse event by the patients affected. In addition, neuropathy is commonly seen during treatment with stavudine (10-20% of treated patients) and has a slow reversibility upon stopping the treatment.

The risk of mitochondrial toxicity for stavudine was already identified at the time of previous renewal. and the CHMP requested on this ground an additional renewal. The toxicity profile of stavudine has been also well characterised in the SmPC.

Since the last renewal for stavudine in 2006, the standard of assessment of HIV medicinal products has evolved, notably due to the approval of a number of new medicines in the European Union for the treatment of HIV (new therapeutic classes e.g. CCR5 antagonists, integrase inhibitors, new molecules in an existing class e.g. protease inhibitors). The approval of these medicines introduced a significant progress in the treatment of HIV due to their therapeutic efficacy and safety profile (notably regarding mitochondrial toxicity)..

Taking into account the data provided as part of this renewal application, the conclusions of the HIV / Anti Viral Scientific Advisory Group (HIV / AV SAG) and the current standard of assessment, the CHMP considered the safety profile of stavudine, especially with regards to the mitochondrial toxicity, justify a restriction of indication. As a consequence, the CHMP concludes that the treatment with stavudine should be restricted to cases where 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 by the CHMP to the shortest time possible. The CHMP furthermore concluded that the treatment with stavudine should be followed by a switch to an alternative appropriate therapy whenever possible and the patients continuing treatment with stavudine should be assessed frequently and switched to an alternative appropriate therapy whenever possible.

The Product Information has been updated accordingly (refer to section 2.5).

Adequate measures to inform stakeholders and gathering of information have been agreed with the MAH (refer to section 2.4.2.4).

The CHMP decided to increase the PSUR submission schedule from a 3 years submission schedule to a 2 years submission schedule and the MAH was requested to submit a Risk Management Plan (RMP).

Overall, the CHMP is of the opinion that the benefit risk balance for stavudine remains positive in this restricted indication and that the renewal can be granted with unlimited validity.

3. Outcome of the renewal

Based on the CHMP review of the available information, the recommendations of the HIV / Anti Viral Scientific Advisory Group (HIV / AV SAG) and on the basis of a re-evaluation of the benefit risk balance in the light of the current standard of assessment, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated in a part of the patient population and therefore considered that the benefit risk balance of Zerit continues to be favourable in a restricted indication.

The CHMP recommends the renewal of the Marketing Authorisation for Zerit, subject to the conditions as laid down in Annex II to the Opinion as well as the commitments of the Marketing Authorisation Holder as laid down in his Letter of Undertaking.

The CHMP is also of the opinion that the renewal can be granted with unlimited validity.

The renewal requires amendments to the terms of the Community Marketing Authorisation.

The following annexes have been amended: Annex I, Annex II.B, Annex IIIA and IIIB.