EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Vistide

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
IB/0039	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits	07/09/2012	n/a		
A20/0035	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17	22/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/121/A-

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).				20/0035
IG/0172	A.7 - Administrative change - Deletion of manufacturing sites	11/05/2012	n/a		
IA/0036	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	09/12/2011	n/a		
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2011	n/a	PL	
II/0032	Following the assessment of PSUR and an increasing off-label use, update of the sections 4.2 and 4.4 of the SmPC to warn that the safety and efficacy has not been demonstrated in diseases other than CMV retinitis in adults with AIDS. The PL has been updated accordingly. Minor linguistic changes are also proposed in the German, Portugal and Sweden PI. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	24/01/2011	SmPC and PL	The assessment of the 13th PSUR for Vistide (covering the period 23 April 2006 to 22 April 2009) highlighted a significant proportion of individual case safety reports received for cidofovir involved off-label use, with 87% of 46 adverse event reports received involving the use of Vistide either in an unapproved indication or via an unapproved route of administration. The most frequent and serious adverse reactions reported for Vistide in off-label indications and routes of administration were renal toxicity, ocular toxicity and neutropenia, which is consistent with the safety profile of Vistide. Lack of effect was frequently reported for patients receiving Vistide for unapproved indications or routes of

					administration and it was noted that a higher proportion of reports of off-label use involved a fatal outcome compared to reports where Vistide was used in accordance with the SmPC (45% versus 27%). In view of these data, the CHMP agreed with the MAH's proposal to update the section 4.4 with addition of a warning that 'The safety and efficacy of Vistide has not been demonstrated in diseases other than CMV retinitis in adults with AIDS'. The section 4.2 was also amended and the Package Leaflet updated accordingly. A DHPC, together with an associated communication plan, was agreed by the CHMP.
IB/0033/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/11/2010	n/a		

IB/0031/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/ immunological medicinal products B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	05/10/2010	n/a		
II/0030	To update sections 4.4 and 4.5 of the Summary of Products Characteristics (SmPC) with a warning on potential increased risk of Fanconi syndrome with the concomitant use of cidofovir and tenofovir following assessment of the 13th PSUR. Sections 2 and 4 of the Package Leaflet (PL) were updated accordingly. In addition, the MAH took the opportunity to update the SmPC to reflect the latest version of the Quality Review of Data (QRD) template. Furthermore, the MAH updated the PL in agreement with the results of the User Testing.	18/02/2010	26/03/2010	SmPC and PL	The assessment of the 13th Periodic Safety Updated Report (PSUR), covering the period from 23 April 2006 to 22 April 2009 showed a series of reports pertain to the concomitant use of cidofovir and tenofovir, and most related to renal dysfunction and Fanconi syndrome. Fanconi syndrome is already included in section 4.8 “Undesirable effects” of the SmPC of both cidofovir and tenofovir. However, as reports have illustrated, concomitant exposure to these compounds is expected to lead to cumulative toxicity. Therefore, a warning regarding the increased risk of Fanconi syndrome with the concomitant use of cidofovir and tenofovir was

	Update of Summary of Product Characteristics and Package Leaflet				included in section 4.4 “Special warnings and precautions for use” of the SmPC. This information was also reflected in section 4.5 of the SmPC “Interaction with other medicinal products and other forms of interaction”.
II/0029	To update section 4.8 of SPC to include diarrhoea as a common adverse reaction. Section 4 of the PL was updated accordingly. The MAH took the opportunity of this variation to reinsert into section 4.4 of the SPC and section 2 of the Package Leaflet a statement concerning barrier contraceptive in men, that was removed by mistake. Furthermore, product information was updated in accordance with version 7.2 of the QRD template Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/09/2009	23/10/2009	SmPC, Labelling and PL	The safety data submitted by the MAH was based on a review made by the MAH. Nineteen cases of spontaneous reports of diarrhoea had been received. In one case the aetiology of diarrhoea was due to a viral infection; in one case diarrhoea was primarily attributed to administration of probenecid. Most of the cases described patients who were severely ill and were receiving multiple treatments that included cidofovir. Some cases reported patients with medical history of diarrhoea. For these cases, as well as for the cases where no more likely aetiology was identified, a role for cidofovir in contributing to the diarrhoea in these patients could not be excluded. Based on these data section 4.8 of SPC was revised to include diarrhoea as a common adverse reaction.
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2009	n/a	Labelling	
IA/0028	IA_09_Deletion of manufacturing site	07/04/2009	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/01/2009	n/a	PL	
IA/0023	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	18/12/2008	n/a	Annex II and PL	
IA/0024	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/12/2008	n/a		

IA/0025	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	18/12/2008	n/a		
T/0022	Transfer of Marketing Authorisation	31/10/2008	28/11/2008	SmPC, Labelling and PL	
II/0021	To update section 4.8 of the SPC, to be in line with the Guideline of Summary of Product Characteristics and QRD templates. This update is further to a CHMP request during the review of variation II/18. Furthermore, upon CHMP request section 4.5 was updated concerning interactions with probenecid and section 4.8 was revised to include information on the safety profile of probenecid. The MAH took also the opportunity of this variation to rephrase a paragraph of section 4.3 of the SPC. Sections 2 "Before you use Vistide" and 4 "Possible side effects" of the package leaflet were updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	The MAH has conducted an updated integrated analysis of the safety data from the three pivotal phase II/III studies (GS-93-105, GS-93-106 and GS-93-107). This integrated analysis includes safety data from 247 patients treated with intravenous cidofovir. Data from GS-95-120 and dose response from GS-93-107 have been used as a supplementary source of information. Based on the result of this analysis the product information was updated as follows: " Headache and chills were introduced as a very common and common adverse reactions respectively " Vomiting was classified as very common instead of common " Pneumonia and infection adverse reactions were removed since it was considered to represent background events of HIV patients and not causally related to cidofovir " Renal failure and Falconi syndrome adverse reactions previously mentioned in the postmarketing reported reactions were included in the table with frequency common and uncommon respectively. This section was completely revised to be in line with Volume 9A, the Guideline of Summary of Product Characteristics and EMEA/QRD template. Upon CHMP request and since cidofovir is administered with

					probenecid to minimise renal toxicity, the product information was updated to include information taken from Martindale on probenecid interactions and safety profile. Furthermore, prescribers are advised to consult the current probenecid SPC (or an appropriate drug reference source) for full information on probenecid.
II/0020	Quality changes	20/09/2007	26/09/2007		
II/0018	To update the SPC to reflect the most up-to-date safety information, further to the assessment of the renewal. The changes relate to concomitant use of cidofovir with other nephrotoxic agents and the occurrence of Fanconi's syndrome and concomitant use of other NRTIs and probenecid. The PL was updated accordingly. Furthermore, SPC, labelling and PL were updated in accordance with the latest QRD templates. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/07/2007	29/08/2007	SmPC, Labelling and PL	Further to the assessment of the renewal, the product information was updated to indicate that the safety of cidofovir has not been evaluated in patients receiving other known potentially nephrotoxic agents such as tenofovir. As cases of Fanconi's syndrome (a kidney disorder which results in decreased reabsorption of electrolytes and nutrients back into the bloodstream) have been reported, it is recommended to discontinue potentially nephrotoxic agents at least 7 days before starting cidofovir. The importance of pre-hydration and the use of probenecid when taking cidofovir was re-emphasised. The warnings section was updated and cidofovir was contraindicated in patients unable to receive probenecid, as the association prevents/reduces nephrotoxicity. The wording regarding administration of cidofovir in renal insufficient/haemodialysis patients was also updated to give guidance to prescribers on how to proceed. The interactions section was updated regarding the concomitant use of other nucleoside reverse transcriptase inhibitors with probenecid, as patients should be monitored for zidovudine induced haematological toxicity when probenecid is also administered. The product information was also brought in line with the current EMEA quality review of documents templates.

R/0017	Renewal of the marketing authorisation.	26/04/2007	08/06/2007		
II/0016	Quality changes	16/11/2006	27/11/2006		
IA/0015	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	27/09/2004	n/a	SmPC, Annex II, Labelling and PL	
II/0014	To update the Summary of Product Characteristics (SPC) section 4.8 (“Undesirable Effects”) to reflect the frequencies of the adverse drug reactions in accordance with the SPC guideline. The frequencies of nephrotoxic effects are presented according to results in clinical trials. In section 6.6 (“ Instructions for handling and disposal”), reference is made to contact the local representative for information in case of difficulty in obtaining probenicid. Relevant changes are also introduced in the Package Leaflet (PL). Moreover, the list of local representatives in the PL has been revised and some editorial changes have been made to the Danish, French and Portuguese translations. Update of Summary of Product Characteristics and Package Leaflet	18/12/2002	17/03/2003	SmPC and PL	
R/0013	Renewal of the marketing authorisation.	25/04/2002	10/07/2002		
I/0010	01_Change following modification(s) of the manufacturing authorisation(s)	01/10/2001	19/02/2002	SmPC and PL	

I/0011	03_Change in the name and/or address of the marketing authorisation holder	01/10/2001	19/02/2002	SmPC, Labelling and PL	
I/0012	11_Change in or addition of manufacturer(s) of active substance	09/11/2001	19/11/2001		
II/0009	The Marketing Authorisation Holder applied for an update of section 4.8 of the SPC and the relevant section of the Package Leaflet concerning the inclusion of new post marketing safety information as outlined in annex 1. Update of Summary of Product Characteristics and Package Leaflet	12/04/2000	13/07/2000	SmPC and PL	
II/0008	The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics and the relevant sections of the Package Leaflet concerning the inclusion of new information regarding nephrotoxicity. Update of Summary of Product Characteristics and Package Leaflet	25/03/1999	17/09/1999	SmPC and PL	
II/0007	Update of section 4.8 (Undesirable effects) of the SPC and the relevant section of the Package Leaflet concerning the inclusion of a statement regarding the potential for iritis/uveitis associated with Vistide. Update of Summary of Product Characteristics and Package Leaflet	19/11/1998	26/02/1999	SmPC and PL	
I/0006	20_Extension of shelf-life as foreseen at time of authorisation	01/07/1998	18/09/1998	SmPC	

I/0005	01_Change following modification(s) of the manufacturing authorisation(s)	01/07/1998	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/04/1998	02/06/1998	Labelling and PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/08/1997	05/11/1997	Labelling	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/1997	n/a	PL	