EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2013
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Assessment report pursuant to Article 29(4) of Directive 2001/83/EC

Didanosine and associated names

INN: didanosine

Applicant: Aurobindo Pharma (Malta) Limited

Procedure no: EMEA/H/A-29/1367

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Aurobindo Pharma (Malta) Limited submitted an application for decentralised procedure of Didanosine and associated names, 200mg, 250mg and 400mg gastro resistant hard capsules on 30 September 2008.

The application was submitted to the reference Member State (RMS): United Kingdom (UK) and the concerned Member States (CMS): France (FR), Germany (DE), Italy (IT), the Netherlands (NL), Portugal (PT), Romania (RO) and Spain (ES).

The Decentralised procedure UK/H/1665/01-03/DC started on 03 March 2009.

On day 210 France and the Netherlands had major issues on bioequivalence which remained unsolved; hence the procedure was referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)), under Article 29, paragraph 1 of Directive 2001/83/EC, by the United Kingdom on 20 December 2012. The CMD(h) 60 day procedure was initiated on 31 December 2012.

Day 60 of the CMD(h) procedure was on 28 February 2013 and since there could be no agreement the procedure was referred to the Committee for Medicinal Products for Human Use (CHMP).

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by the United Kingdom on 04 March 2013, France and the Netherlands raised public health objections as they considered that the bioequivalence has not been shown under fed conditions, indicating that the quality of the test formulation differs from the reference medicinal product.

2. Scientific discussion during the referral procedure

2.1. Introduction

Didanosine (2', 3'-dideoxyinosine) is an inhibitor of the in vitro replication of human immunodeficiency virus (HIV) in cultured human cells and cell lines. After didanosine enters the cell, it is enzymatically converted to dideoxyadenosine-triphosphate (ddATP), its active metabolite. In viral nucleic acid replication, incorporation of this 2', 3'-dideoxynucleoside prevents chain extension, and thereby inhibits viral replication. In addition, ddATP inhibits HIV-reverse transcriptase by competing with deoxyadenosine-triphosphate (dATP) for binding to the enzyme's active site, preventing proviral DNA synthesis.

Didanosine and associated names is indicated in combination with other antiretroviral drugs for the treatment of HIV-1 infected patients.

The reference product in EU is Videx EC (200, 250 and 400 mg) hard capsules, first authorised in the UK on 19 September 2000.

The application for Didanosine and associated names was initially submitted by the applicant under the legal basis of the Article 10.1 of Directive 2001/83/EC. However, after the CMDh meeting in February 2013 the legal basis was changed by the applicant to the Article 10.3 of Directive 2001/83/EC in all Concerned Members States (CMSs).

During the decentralised procedure France and the Netherlands expressed the opinion that bioequivalence had not been demonstrated in the fed conditions as C_{max} (Concentration maximal) was outside the 80-125% acceptability limits. In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence[1], for modified release formulation, the test product should meet the defined criteria for both C_{max} and AUC (Area Under the Curve) in both fasted and fed bioequivalence studies, in order to conclude a similar efficacy and safety between the applied product and the reference product. In addition, the objecting Members States considered that the arguments provided by the applicant did not sufficiently address the consequences of the difference observed in didanosine pharmacokinetics in the fed state between test and reference products.

The decentralised procedure was closed on day 210, with most of the CMSs agreeing with the conclusions of the RMS's assessment report except France and the Netherlands which raised a potential serious risk to public health (PSRPH). A referral was thus triggered at the CMD(h). The major concern raised by France and the Netherlands could not be solved during the CMD(h) referral and the issue was therefore referred to the CHMP.

2.2. Critical evaluation

In order to demonstrate the safety and efficacy of Didanosine and associated names in combination with other antiretroviral drugs in the treatment of HIV-1 infected patients, the application dossier was based on two single dose bioequivalence studies, one under fasting state and one under fed state. Both studies were carried out using open label, randomised, two treatment, two sequence, two period, single dose cross-over design. Didanosine and associated names (Gastro-resistant capsules 400 mg) was compared to the reference product Videx EC (Gastro-resistant capsules 400 mg) in 60 healthy adults under fasting conditions. The fed study was conducted during an extended clock-stop.

Results of the bioequivalence studies

The primary pharmacokinetic parameters (C_{max} and AUC) were satisfactory in the fasting study with the 90% confidence interval (CI) falling within the standard criteria of 80.00 – 125.00%.

In the fed study, the results were satisfactory in terms of extent of absorption (i.e. AUC) with 90% CI within standard range of 80.00 – 125.00%. However, the 90% CI for C_{max} was outside the standard criteria. The observed 90 % CI for C_{max} in the fed study was 100.36 – 132.76%. It is acknowledged that these results are outside the standard range of 80 – 125%; however these are within the wider acceptance criteria of 70 – 143% which may be used for highly variable drugs. Of note, bioequivalence in fasted state is considered to be the most important as this product is intended to be taken on an empty stomach.

The table below presents the mean pharmacokinetic parameters (± SD) and 90% CI obtained in the two bio-equivalence studies involving Didanosine and associated names.

[1] Note for Guidance on the investigation of bioavailability and bioequivalence (EMA/CPMP/EWP/QWP/1401/98)

Table 1: Mean pharmacokinetic parameters (± SD) and 90% CI obtained in the two bio-equivalence studies involving Didanosine and associated names

Parameters	*Fasting Study (Study No. 063/08)*		*Fed Study (Study No. 450/10)*	
	Test (B.No. DL4007001)	*Reference (B.No. 0264)*	*Test (B.No. DU4010001)*	*Reference (B.No. A340)*
C_{max} (ng/mL)	**812.543** ± 280.7708	**871.989** ± 439.0591	**429.031** ± 161.6541	**389.987** ± 182.8906
AUC_{0-t} (hr.ng/mL)	**2765.209** ± 897.8424	**2698.901** ± 1161.2623	**1967.315** ± 562.6344	**1880.291** ± 591.1757
AUC_{0-inf} (hr.ng/mL)	**2777.384** ± 897.6537	**2710.068** ± 1161.1934	**1978.927** ± 562.2921	**1891.600** ± 591.2156
T_{max} (hr)	2.75	2.00	5.52	5.77
T_{half}	1.976	2.053	2.143	2.019
90% CI for Cmax (T/R Ratio %)	90.68 – 110.99 (100.32)		100.36 – 132.76 (115.43)	
90% CI for AUC_{0-t} (T/R Ratio %)	100.46 – 114.19 (107.11)		97.43 – 117.40 (106.95)	
90% CI for AUC_{0-inf} (T/R Ratio %)	100.49 – 114.12 (107.09)		97.45 – 117.27 (106.90)	

Scientific discussion

Dosing recommendations for didanosine

Didanosine is intended to be administrated on en empty stomach as stated in the proposed Summary of Product Characteristics (SmPC): "*Didanosine absorption is reduced in the presence of food, and hence Didanosine gastro-resistant capsules should be administrated on an empty stomach (at least 2 hours before or 2 hours after a meal)*". Pharmacokinetics studies conducted on Didanosine formulations reveal that administration of the product with food or immediately after food results in decreased in vivo availability of the drug. Since the product is to be administrated at least 2 hours before or after food intake, it is unlikely that the product ingested will be exposed to in vivo conditions, prevailing under fed state.

Observed food effect for test and reference products

As per the current recommendations for modified release formulations[1,2], bioequivalence studies in fasted and fed conditions are required. The main purpose of conducting a bioequivalence fed study is to exclude food related effects, such as dose-dumping (in particular for gastro-resistant formulations) or failure of protection from acid mediated degradation in the stomach.

The administration of the reference product with a high fat meal significantly decreases the AUC (19%) and C_{max} (46%) of didanosine. This observation is in line with the results presented in the current application where AUC and C_{max} of the test product significantly decrease under fed conditions. Therefore, for both the test and the reference product in the fed state the absorption of didanosine decreases which indicate that both products possess similar food effect in terms of reduction in C_{max} and AUC with no evidence of dose-dumping. The only difference is the magnitude of the decrease, which is less for the test than for the reference product.

The applicant claimed that the significant decrease observed under fed conditions for C_{max} for the test product (90% CI outside the standard range) may be attributed to high inter-individual variability with respect to C_{max} which was 36% in the study conducted under fed conditions. Considering this, the

[2] Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96/Corr1)

sample size that may be required to meet the standard bio-equivalence criteria would be as high as 232 subjects to obtain power of at least 80%.

The presented data does not give evidence of in vivo dose-dumping from the formulation under fed conditions. Hence, both test and reference products can be considered as having similar food effect in terms of reduction in C_{max} and AUC.

Clinical significance of Cmax with didanosine

Mechanism of action of didanosine

Didanosine belongs to the class of Nucleoside Reverse Transcriptase Inhibitors (NRTI). Didanosine has to be first converted intracellularly to its active metabolite ddATP (responsible for antiviral activity) which has a significantly longer intracellular half-life (about 43 hours) as compared with plasma half-life of didanosine. The surrogate markers of efficacy in HIV-infection are virological/immunological parameters like RNA load, CD4 cell counts and p24 antigen some of which are related to extent of exposure (i.e. AUC). Based on certain literature references, the applicant claimed that differences in plasma concentrations of didanosine are not of clinical relevance as such since it may not result in changes in the intracellular triphosphate concentrations. Therefore, minor variations in plasma concentrations are not likely to impact the antiviral activity. The applicant substantiated this understanding based on the following discussion with reference to alternate formulations of didanosine and literature data available on food effect.

Reference to different formulation of didanosine on the market

Initial clinical trials demonstrating efficacy of didanosine in treatment of HIV infecting were conducted using buffered tablets[3,4,5,6,7,8]. The pharmacokinetics data reveals that the plasma concentration (C_{max}) obtained from enteric-coated capsule formulation of didanosine is about 40% lower as compared to the buffered tablet formulation. This is attributed to the delay in absorption rate of enteric coated formulation which is reflected in the T_{max} which is about 2 hours for the enteric coated formulation compared to 0.67 hours for the buffered tablet. However, both formulations are equivalent in terms of extent of absorption (i.e. AUC). Therefore, it is considered that the fact that both formulations have been used for the same indications and at similar doses suggests that AUC is more relevant for ensuring efficacy of didanosine in antiviral therapy, and the changes in C_{max} are unlikely to compromise antiviral efficacy.

Discussion on literature reports related to food effect of didanosine

The applicant provided literature references which showed that for the action of Didanosine, AUC is the most important parameter[9,10,11,12,13]. Irrespective of whether Didanosine is taken with or without food,

[3] Damle BD et al. Pharmacokinetics and gamma scintigraphy evaluation of two enteric coated formulations of didanosine in healthy volunteers. Br J Clin Pharmacol. 2002a; 54: 255-61
[4] Damle BD et al. Bioequivalence of two formulations of didanosine, encapsulated enteric-coated beads and buffered tablet, in healthy volunteers and HIV-infected subjects. J Clin Pharmacol. 2002b; 42:791-797
[5] Beltangady M et al. Relation between plasma concentrations of didanosine and markers of antiviral efficacy in adults with AIDS and AIDS related complex. Clinical Infectious Diseases 1993; 16: S26-S31
[6] Drusano GL et al. Relationship between dideoxyinosine exposure, CD4 counts and p24 antigen levels in HIV infection. Ann Intern Med 1992: 116:562-566
[7] Perry CM, Balfour JA. Didanosine: An Update on its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy in the Management of HIV Disease. Drugs. 1996); 52: 929-962
[8] Schrader S et al. Comparison of HIV RNA suppression produced by triple regimens containing either didanosine enteric-coated or didanosine tablet formulations each administered once daily. Abstract 318. Paper presented at 8th conference on Retrovirus and opportunistic infections. Chicago 2001
[9] La Porte C et al. Pharmacokinetic interaction study of indinavir/ritonavir and the enteric-coated capsule formulation of didanosine in healthy volunteers. J Clin Pharmacol. 2005; 45: 211-218
[10] Lopez JC et al. A Cohort Study of the Food Effect on Virological Failure and Treatment Discontinuation in Patients on HAART Containing Didanosine Enteric-Coated Capsules (FOODDIe Study). HIV Clin trials. 2006; 7: 155-162
[11] Hernandez-novoa B et al. Effect of food on the antiviral activity of didanosine enteric-coated capsules: A pilot comparative study. HIV Medicine. 2008; 9: 187-191.

the virological response is based on the total drug exposure. In the current application, the AUC under both fasted and fed conditions was within the acceptance criteria of 80-125%.

2.3. Recommendation

Having considered the results of the bioequivalence studies and data from the literature, the CHMP is of the opinion that there is sufficient evidence to support the safety and efficacy of Didanosine and associated names, 200, 250, 400 mg gastro resistant hard capsules.

Therefore, the CHMP recommended the granting of the marketing authorisation for Didanosine and associated names, 200, 250, 400 mg gastro resistant hard capsules.

2.4. Conclusions and benefit risk assessment

Whereas

- The Committee considered the notification of the referral triggered by the United Kingdom under Article 29(4) of Directive 2001/83/EC. The Netherlands and France considered that the granting of the marketing authorisation constitutes a potential serious risk to public health.
- The Committee reviewed all the data submitted by the applicant in order to support the bioequivalence between Didanosine and associated names and the reference product.
- The Committee is of the opinion that bioequivalence has been demonstrated under fasting conditions which is the recommended state for administration of didanosine.
- The Committee noted that in the fed study, both formulations were subject to a food effect reducing plasma concentrations. The bioequivalence studies confirmed that dose dumping did not occur with Didanosine and associated names. The results were satisfactory in terms of extent of absorption (i.e. AUC). The Committee acknowledged that the conventional criterion for bioequivalence for maximum plasma concentration (C_{max}) was outside the 80-125% acceptability limits. However, the observed effect of food is lower and the Committee is of the opinion that this is not clinically relevant based on considerations relating to the mechanism of action and, in particular, that Didanosine and associated names is to be administrated on an empty stomach.

the CHMP was of the opinion that the benefit/risk ratio of Didanosine and associated names is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.

[12] Berenguer J et al. Didanosine, Lamivudine, and Efavirenz versus Zidovudine, Lamivudine, and Efavirenz for the Initial Treatment of HIV Type 1 Infection: Final Analysis (48 Weeks) of a Prospective, Randomized, Noninferiority Clinical Trial, GESIDA 3903 HIV/AIDS. CID 2008; 47: 1083-1092.
[13] Stevens RC et al. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. AIDS Res Hum Retroviruses. 2000; 16: 415-421