CLINICAL REVIEW

Application Type	NDA 21-183
Submission Number	020
Submission Code	SE5
Letter Date	March 31, 2008
Stamp Date	April 1, 2008
PDUFA Goal Date	October 1, 2008
Reviewer Name	Charu J. Mullick
Review Completion Date	September 17, 2008
Established Name	Didanosine
Trade Name	VIDEX® EC
Therapeutic Class	Nucleoside Reverse Transcriptase Inhibitor
Applicant	Bristol-Myers Squibb Company
Priority Designation	P
Formulation	Enteric-coated capsule (125, 200, 250, 400 mg)
Dosing Regimen	200 mg once daily for body weight less than 25 kg, 250 mg once daily for body weight 25-60 kg, 400 mg once daily for body weight at least 60 kg
Indication	VIDEX® EC (didanosine, USP), in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus-1 infection
Intended Population	HIV-1-infected pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The approval of Videx EC, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in pediatric patients weighing 20 kg or more is recommended. This approval will provide pediatric patients with a convenient once daily dosing alternative to the currently approved twice daily dosing regimen required for pediatric powder for oral solution. In addition, data from a healthy volunteer hepatic impairment study was added to the label; this study confirmed that no changes in didanosine pharmacokinetics are observed with hepatic impairment.

The enteric-coated formulation of didanosine, Videx EC, is approved currently for adults only. Twice daily dosing of Videx pediatric powder for oral solution is approved currently for pediatric patients. The recommendation for approval of Videx EC for pediatric patients is based on comparison of pharmacokinetics of Videx EC in adult and pediatric patients, comparison of proposed pediatric doses to approved pediatric doses for Videx pediatric powder for oral solution and simulations of Videx EC exposures in pediatric patients. The comparison of pharmacokinetic exposures of Videx EC between adult and pediatric populations from historical clinical trials formed the basis of this review. A review of pharmacokinetic data from seven pediatric and two adult didanosine trials by the Applicant and FDA lead to the derivation of Videx EC doses for different pediatric weight groups.

Safety and efficacy data for 831 pediatric subjects, age 3 months to 18 years, receiving Videx pediatric powder for oral solution was previously reviewed by FDA and formed the basis for approval of new dosing recommendations for Videx pediatric powder for oral solution in 1996. Because the recommended pediatric doses for Videx EC formulation are expected to provide pharmacokinetic exposures that fall within the range observed with the currently marketed pediatric powder formulation, no additional safety or activity data were required for this review.

This submission addresses the following outstanding post-marketing commitment for Videx EC issued on October 31, 2000:

> The evaluation of the pharmacokinetics and safety of Videx EC in appropriate pediatric populations.

Of note, this requirement was waived for children under the age of six years due to the enteric-coated nature of Videx EC formulation and the inability of younger children to reliably swallow an intact capsule.

1.2 Recommendation on Post marketing Actions

1.2.1 Risk Management Activity

A risk management plan was not submitted with this application. The risk assessments based on available data indicate routine post-marketing pharmacovigilence activities suffice as tools to identify potential risks for Videx EC in children. No additional risk minimization activities are required.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Conversion of Dosing from Body Surface Area to Body Weight Based

The pediatric doses proposed for Videx EC were derived through pharmacokinetic modeling. Pooled plasma concentration-time data from seven pediatric and two adult clinical trials were used to create a population pharmacokinetic model that scaled all pharmacokinetic parameters for weight; the model was used to simulate different weight-based pediatric doses of Videx EC. Videx pediatric powder is currently approved for pediatric use in doses based on body surface area (BSA) whereas the current adult dosing for Videx EC is based on body weight (BW). In the review of this supplement, a comparison was performed by FDA clinical pharmacology reviewer between approved BSA-based doses and *proposed* BW-based doses using data collected in pediatric trials. The Applicant's proposed dose for the weight group 20-25 kg was accepted, however, BSA-BW dose comparisons performed by FDA revealed BW-based doses were lower by 13-20% than approved pediatric BSA doses for the weight group 25-60 kg. A new dosing scheme for the 25-60 kg weight group was explored by the clinical pharmacology review team. The exploration led to the consideration of 250 mg Videx EC dose for 25-30 kg group, and 325 mg Videx EC dose for 35-60 kg group based purely on pharmacokinetic data. The dose recommendation of 250 mg Videx EC for 20-25 kg group was determined to be clinically acceptable. However, the choice of 325 mg Videx EC for the 35-60 kg group was not considered acceptable in the absence of supportive efficacy and safety evidence. The final dose recommendation for 25-60 kg weight group is 250 mg Videx EC.

1.3.2 Activity

The efficacy of Videx EC for treatment of HIV-1 infection in adults was established in 2000. In general, efficacy of HIV antiretrovirals in the pediatric population is extrapolated from adult studies and supported with activity data from pediatric clinical trials. Adequate efficacy and safety data from 831 pediatric patients receiving Videx pediatric powder for oral solution was previously submitted to FDA in support of the approval of new dosing recommendations for Videx pediatric powder in 1996. Therefore, no new activity data was submitted in this application or required for review.

The Applicant simulated various body weight-based doses of Videx EC in different dose groups to match the adult didanosine area-under-curve (AUC) exposure from a reference didanosine study AI454157. Overall, a comparison of adult and pediatric pharmacokinetic parameters revealed an overlap of didanosine peak, trough and AUC among adult and pediatric subjects receiving Videx EC. For subjects weighing 25-30 kg, utilization of the FDA recommended 250 mg dose of Videx EC provided exposures closer to adult target efficacy exposure; this is reflected in the final dosing recommendation. The antiviral effectiveness of Videx EC in children is thus based on established adult efficacy and previously observed antiviral activity in pediatric patients using the pediatric powder formulation.

1.3.3 Dosing Regimen and Administration

The recommended pediatric dosing for Videx EC differs from currently approved didanosine dosing in children as follows:

1. The recommended dosing scheme is based on body weight,
2. The recommended dosing scheme provides a once daily dosing alternative to the currently approved twice daily dosing required for the pediatric powder for oral solution,
3. Children weighing less than 20 kg will not be able to take Videx EC, because children weighing less than 20 kg fall into an age range that cannot be expected to consistently swallow an intact capsule.

The Applicant's proposed dosing scheme was modified by the clinical pharmacology team following review of pharmacokinetic data. Table 1 presents the final dosing recommendation.

Table 1: Final dose recommendation for Videx EC in pediatric patients

Body weight	Dose of Videx EC
20 to less than 25 kg	200 mg of Videx EC once daily
25 to less than 60 kg	250 mg of Videx EC once daily

1.3.4 Safety

No new safety data was submitted in the sNDA. No safety concerns were raised with this sNDA because the proposed Videx EC doses provide targeted didanosine exposures that fall within

exposures observed with approved doses of Videx pediatric powder. The key historical comparator is Study ACTG152 conducted between 1991 and 1995 in 831 subjects of ages 3 months to 18 years. The efficacy and safety findings from this multicenter trial supported approval of dosing recommendations for Videx pediatric powder for oral solution. Importantly, the peak plasma concentration C_{max} for Videx EC formulation is reduced approximately 40% relative to didanosine buffered powder for pediatric patients. Hence, new safety concerns are not anticipated with the recommended pediatric dosing. Of note, the reduced C_{max} associated with Videx EC formulation will not impact efficacy because the recommended pediatric doses of Videx EC were derived from established adult efficacy exposures.

1.3.5 Drug-Drug Interactions

No new drug-drug interactions were described for didanosine in this sNDA.

1.3.6 Special Populations

The sNDA addresses two special groups of patients, namely, pediatric population and patients with hepatic impairment. The results from a hepatic impairment study, AI454-186, included in this sNDA demonstrated similar mean plasma concentration-time profiles of didanosine between HIV-negative subjects with and without hepatic impairment. Hepatic impairment was not expected to affect didanosine pharmacokinetic profile because this drug is a nucleoside reverse transcriptase inhibitor metabolized by endogenous purine metabolic pathways and excreted primarily via kidney. Study AI454-186 demonstrated hepatic impairment does not alter pharmacokinetics of didanosine and dose adjustment is not necessary in individuals with hepatic impairment.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Videx or didanosine (ddI) was originally approved for use in adults and pediatric patients in 1991 as Videx chewable/dispersible buffered tablets, Videx buffered powder for oral solution, and Videx pediatric powder for oral solution. Videx pediatric powder for oral solution is currently approved for use in children 2 weeks of age or older. All buffered formulations of Videx required concomitant administration with antacid to avoid degradation by gastric acid. In 2000, the enteric-coated formulation, Videx EC, was approved for use in HIV-infected adults. In Videx EC, the active ingredient, didanosine is protected against gastric acid degradation by the use of an enteric coating on the beadlets in the capsule. Unlike the previous buffered preparations, Videx EC eliminated undesirable drug-drug interactions related to the buffer, improved tolerability and allowed for once daily dosing based on body weight. Videx EC is available as 125, 200, 250, 400 mg strength capsules. The approved adult doses for Videx EC and approved pediatric doses for Videx pediatric powder are outlined in Table 2.

Table 2: Current dosing recommendations for Videx pediatric powder and Videx EC

Pediatric Dosing: Videx pediatric powder for Oral solution		**Adult Dosing: Videx EC**	
2 wks to 8 months	100 mg/m^2 BID	Body weight <60 kg	250 mg QD
>8 months	120 mg/m^2 BID	Body weight ≥60 kg	400 mg QD

The applicant seeks pediatric approval for Videx EC. This review describes the supporting pharmacokinetic data and results of simulation analyses submitted by the Applicant, as well as FDA analyses and recommendations.

2.2 History of Videx Dosing in Pediatric Patients

The original approval of Videx in 1991 was based on adult and pediatric Phase 1 studies. A total of 98 subjects were evaluated in two pediatric Phase 1, open-label, dose escalation studies in asymptomatic HIV-infected subjects receiving didanosine doses from 60 to 540 mg/m^2/day. Based on an increased incidence of pancreatitis observed at higher doses, doses in subjects receiving didanosine greater than 360 mg/m^2/day were reduced. In pediatric subjects, pancreatitis occurred in two of 60 subjects (3%) treated with doses below 300 mg/m^2/day and in 5 of 38 subjects (13%) treated with higher doses. Subsequently, pediatric dosing was revised to the current dosing recommendation based on safety and efficacy of didanosine demonstrated in Study ACTG152 conducted between 1991 and 1995 in 831 subjects, ages 3 months to 18 years. In this multicenter, double-blind study, symptomatic HIV-infected children older than 3 months were randomized to receive zidovudine (180 mg/m^2 QID), didanosine (120 mg/m^2 BID), or zidovudine (120 mg/m^2 BID) plus didanosine (90 mg/m^2 BID). A significantly higher risk of HIV disease progression or death in the zidovudine arm lead to unblinding of the trial and discontinuation of that treatment arm. The final analysis of didanosine alone compared to combination therapy did not reveal a significant difference in primary endpoints. The current dosing recommendations for Videx pediatric powder for oral solution are presented in Table 2.

2.3 Currently Available Treatment for Pediatric Population

Combination antiretroviral therapy is the standard of care in pediatric HIV-infected patients. Antiretroviral regimens comprising protease inhibitors or non-nucleoside reverse transcriptase inhibitors in combination with nucleoside reverse transcriptase inhibitors have become the mainstay of highly active antiretroviral therapy in this population. Despite tremendous progress in treatment of HIV infection, a number of challenges remain including the development of resistance to currently approved agents and the significant adverse effects associated with these drugs. A need for new drugs with improved tolerability, convenient dosing, and superior toxicity and resistance profiles remains critical. The currently approved antiretroviral agents for treatment of pediatric HIV infection belong to four classes including nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and fusion inhibitor (Table 3).

Table 3: Currently Approved Antiretroviral Agents for Pediatric Patients

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT or ZDV)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine	Viramune®
	Efavirenz	Sustiva®
PI	Ritonavir	Norvir®
	Nelfinavir	Viracept®
	Fosamprenavir	Lexiva®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Atazanavir	Reyataz®
	Tipranavir	Aptivus®
Fusion Inhibitor	Enfuvirtide (T-20)	Fuzeon®

3 DATA SOURCES AND REVIEW STRATEGY

The chief source of data for this review was pooled plasma concentration-time data from seven pediatric and two adult clinical trials. A total of 2011 plasma concentration-time data points from 151 subjects were utilized to create a population pharmacokinetic model. The age of subjects ranged from Day 1 after birth up to 50 years old; the body weight of subjects ranged from 2.3 to 111 kg. Brief descriptions of the study design and dosing conditions of each study providing pharmacokinetic data are provided in Table 4. Data from pediatric subjects receiving Videx EC formulation was available from two pediatric studies, ACTG403 and PACTG1021. Study ACTG403 was a Phase 2, open-label, multicenter, randomized study designed to evaluate the efficacy, safety, and tolerability of two combination treatments consisting of didanosine with ritonavir and nelfinavir [Arm A] and stavudine with nelfinavir and nevirapine [Arm B] in HIV-infected pediatric subjects. The dose of didanosine was 240 mg/m^2 QD with pediatric powder for oral solution and didanosine EC formulations. Study PACTG1021 is an ongoing Phase 1/2 open-label study to evaluate the safety, tolerability, antiviral activity and pharmacokinetics of emtricitabine in combination with efavirenz and didanosine (didanosine dose of 240 mg/m^2 QD up to a maximum of 400 mg QD) in HIV-infected pediatric subjects. Both didanosine pediatric powder for oral solution and didanosine EC capsules are used in this study.

Table 4: Summary of Videx Clinical Trials providing Pharmacokinetic Data for Analysis

Study (Number of subjects)	Formulation	Dose	Regimen	PK Sampling	LLQ (ng/ml)	Age Range
AI455-094 (n=18)	Solution	120 mg/m^2	BID	Up to 6 samples per subject during 0-8 hours post dose	3 *RIA	1-21 days
HIV-NAT007 (n=8)	Solution	100 mg/m^2	QD	Up to 5 samples per subject during 0-10 hours post dose	3 RIA	14-28 days
DDI-BR001 (n=22)	Solution	180 mg/m^2 90 mg/m^2	QD BID	Sampled at 0.5, 1, 3 hours post morning dose	3 RIA	1-11 years
ACTG403 (n=8)	EC-capsule	240 mg/m^2	QD	Up to 6 samples per subject during 0-12 hours post dose	3 RIA	4-12 years
PACTG-1021 (n=35)	Solution EC-capsule	240 mg/m^2	QD	Up to 6 samples / subject / formulation during 0-24 hours post dose	10 LC-MS	3-21 years
AI454-003 (n=16)	Solution	80-180 mg/m^2	BID	Up to 8 samples per subject during 0-9 hours post dose	25 LC	0.7-11 years
AI454-005 (n=4)	Solution	80-180 mg/m^2	BID	Up to 8 samples per subject during 0-9 hours post dose	25 LC	8-17 years
AI-454-002 (n=10)	Solution	0.8-6 mg/kg	BID	Up to 12 samples per subject during 0-12 hours post dose	25 LC	>18 years
AI454-157 (n=30)	EC-capsule Tablet	400 mg	Single dose	Up to 20 samples per subject per formulation during 0-12 hours post dose	5 RIA	>18 years

Source: Applicant's Modeling and Simulation Report, NDA 21-183 SE5-020

4 CLINICAL PHARMACOLOGY

This section provides a summary of the Applicant's submission as well as analyses performed by FDA clinical pharmacology team. Please refer to FDA Clinical Pharmacology Review of NDA 21-183 SE5-020 by Dr. Nitin Mehrotra for details.

This review provides support for use of Videx EC in pediatric patients by addressing two key concerns:

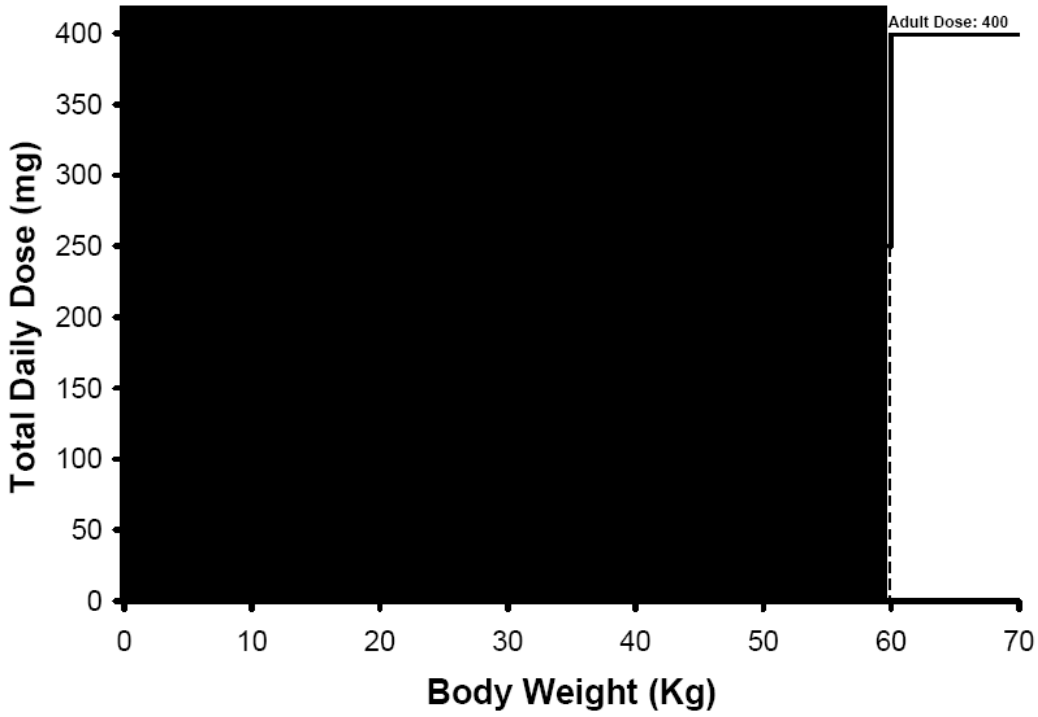
- Conversion of mg/m^2 dosing of the pediatric powder to mg/kg dosing of Videx EC
- Exposure of didanosine achieved after administration of Videx EC in children weighing greater than 20 kg

Plasma concentration data of didanosine acquired from nine clinical trials was incorporated into a meta-analysis to create a population pharmacokinetic model. The model provided simulations and allowed analyses of newly available and historical pharmacokinetic data in adult and pediatric patients who received the Videx pediatric powder formulation to predict the didanosine exposures of Videx EC. The data providing input to the model were scaled for body weight. Based on model based simulation, the Applicant proposed a body weight-based dosing strategy of Videx EC in pediatric patients >20 kg (Table 5 and Figure 1).

Table 5: Applicant's Proposed Pediatric Dosing Scheme for Videx EC

Body weight (Kg)	Total Daily Dose
20 to less than (b)(4) kg	200 mg once daily of Videx EC
(b)(4) to less than 60 kg	250 mg once daily of Videx EC
At least 60 kg	400 mg once daily of Videx EC

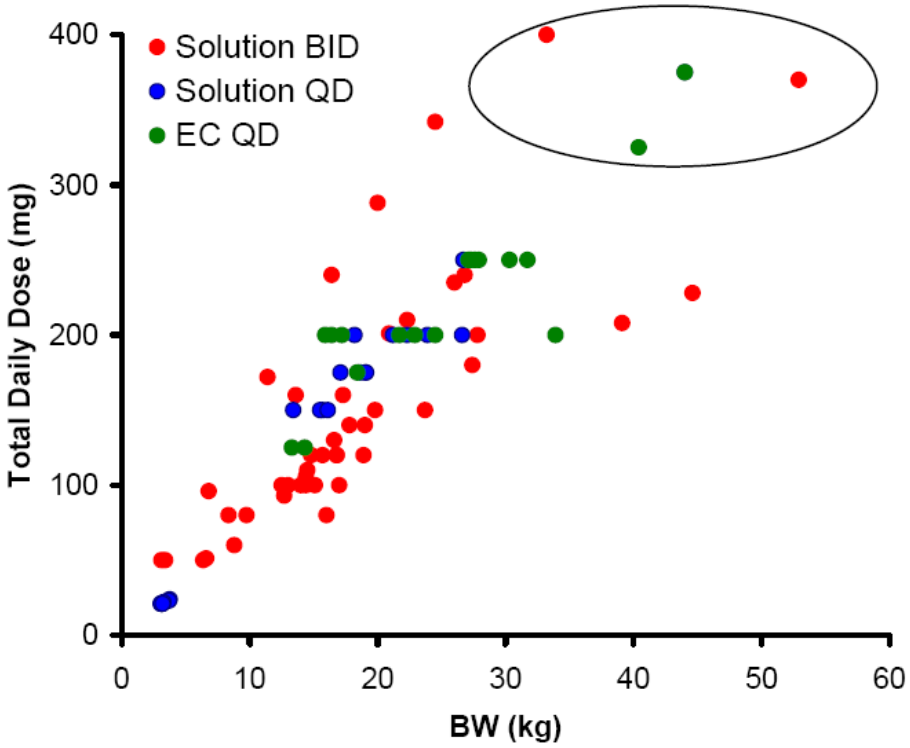
Figure 1: Schematic Representation of the Applicant's Proposed Dosing Strategy



FDA review included a comparison of the approved BSA-based dosing and the Applicant's proposed BW-dosing. This was accomplished by analysis of BW-based dosing of Videx EC in pediatric subjects in the submitted data and comparison with historical data from Study ACTG152. Study ACTG152 was selected because the current pediatric dosing for Videx powder is based on findings from this trial conducted in 831 subjects, ages 3 months to 18 years.

One discrepancy between BSA-based dosing and BW-based dosing is related to capping of maximum approved adult doses for Videx EC. For example, the approved dose of Videx EC for adults weighing 30-60 kg is 250 mg/day; however, the maximum dose of Videx pediatric powder based on BSA for children is 240 mg/m^2 which calculates to dose of 268 mg/day for a subject weighing 30 kg. The difference in dosing represents a capping effect of the Videx EC dose of 250 mg. As shown in Figure 2, the Videx EC dose was capped at 250 mg total daily in the majority of subjects weighing up to 60 kg; the dose changed to 400 mg for > 60 kg subjects. Videx EC doses equivalent to 240 mg/m^2 that were greater than 250 mg were administered only to four pediatric subjects in trials ACTG403 and PACTG1021 (circled in Figure 2). The capping of didanosine doses at 250 mg/day for pediatric subjects with BW <60 kg is based on approved adult doses of Videx EC based evaluated in adult clinical trials.

Figure 2: Distribution by Body weight and Total Daily dose of Didanosine in Pediatric subjects < 60 kg



A review of the Applicant's comparison of Videx EC to BSA-based dosing for pediatric powder revealed lower doses for body weight groups <10 kg and 20-60 kg. Didanosine dosing for pediatric patients weighing <10 kg does not apply to this supplement because the enteric-coated Videx EC capsule cannot be administered to patients who are unable to swallow (age less than 6 years correlating with body weight less than 20 kg); refer to clinical pharmacology review for a detailed discussion related to weight group <10 kg. For weight group 25-60 kg, the Applicant's proposal would provide Videx EC doses as low as 30% of the current approved pediatric dosing as illustrated in Figure 3. The FDA clinical pharmacology review involved an exploration for new doses for the 25-35 kg and 35-60 kg weight groups. The modified dosing scheme (Table 6) proposed by the clinical pharmacology team proposed the 250 mg dose for 20-25 kg group and 325 mg dose for 25-60 kg group; these proposed doses provide closer approximation to the approved BSA-based dosing.

Figure 3: BSA-based dosing Compared to Proposed BW-based dosing for Weight Group 20-60 kg (a) Observed data from ACTG403 and PACTG1021 (b) Observed data from ACTG152
(Red, blue and green circles represent patients in 20-25, 25-30 and 30-60 kg weight group, respectively)
Source: Clinical Pharmacology Review for NDA 21-183 SE5-020

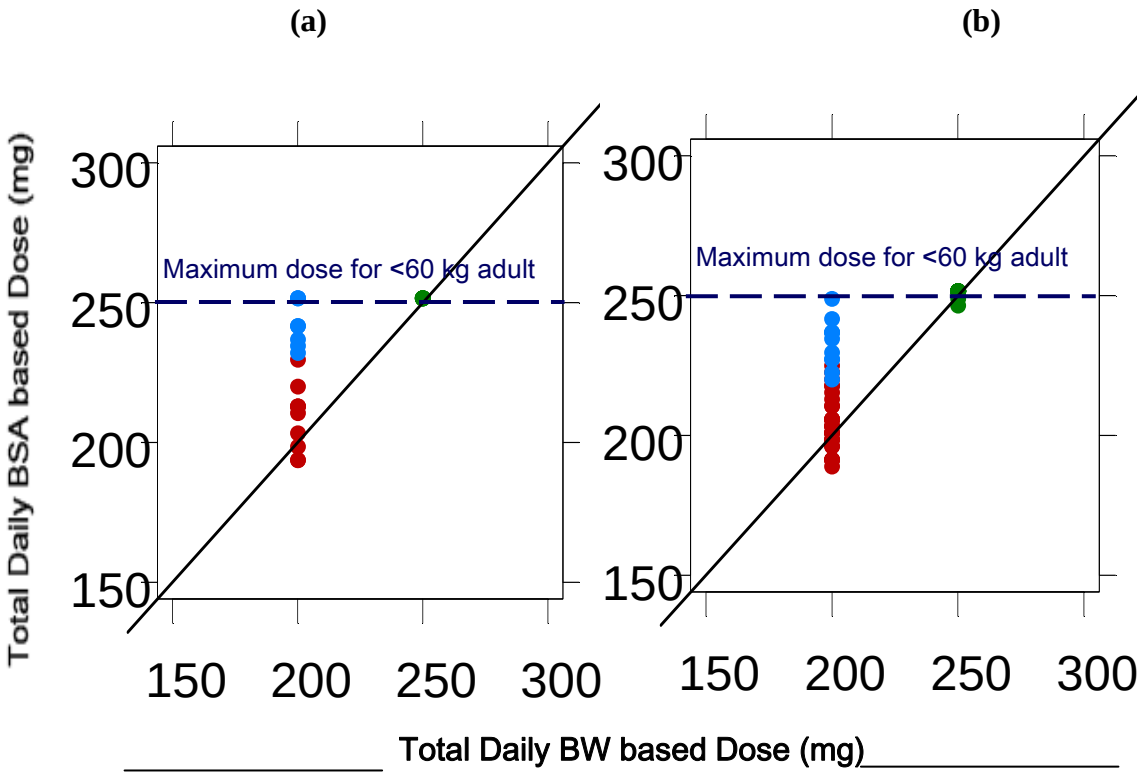


Table 6: Proposed Modification of Body Weight Dosing Scheme for Didanosine by Clinical Pharmacology Team

Body weight (Kg)	Total Daily Dose
20 to less than 25 kg	200 mg
25 to less than 35kg	*250 mg*
35 to less than 60kg	*325 mg*

The 325 mg exploratory dose for 35-60 kg weight group was not considered acceptable. The exploratory dosing scheme was carefully reviewed by the Division particularly in the context of findings from historical Videx clinical trials. One of the key considerations was the appropriateness of 325 mg total daily dose of Videx in pediatric patients weighing 35-60 kg, and whether this dose had been previously evaluated in didanosine trials. The doses of Videx approved originally in 1991 were higher than current recommendations for both adults and pediatric population. The toxicity profile of didanosine, specifically related to risk of pancreatitis and peripheral neuropathy, was the primary reason for dose reduction over time. The dosing recommendations were revised in 1992 based on results of adult trials ACTG 116B and 117.

These trials enrolled 913 subjects in two weight-based cohorts (BW less than or greater than 60 kg) evaluating two doses of Videx buffered powder for oral solution. No advantage was demonstrated with the higher of the two doses with respect to the incidence of AIDS defining events or death. A superior safety profile was observed in the lower dose cohort (167 mg BID for BW < 60 kg and 250 mg BID for BW > 60 kg), specifically the incidence of pancreatitis was 7% in the low dose cohort compared to 13% to the high dose cohort. Accordingly, didanosine dose recommendations were modified (Table 7) in 1992.

Table 7: Revision of Recommended Dose of Didanosine based on ACTG116B/117 (1992)

Patient Weight	Videx Tablets*	Videx Buffered Powder
At least 60 kg	200 mg BID	250 mg BID
< 60 kg	125 mg BID	167 mg BID

*Maximum total daily dose of Videx tablet is 250 mg/day or 400 mg/day depending on body weight

Thus, based on clinical trial data, the options for adult dosing with Videx buffered tablets are limited to 250 mg/day for individuals with BW <60 kg or 400 mg/day for individuals with BW > 60 kg. Of note, the approved daily dose of Videx EC matches these total daily doses of Videx tablets for the two BW categories. In earlier trials, the possibility of a didanosine dose 325 mg/day for subjects weighing between 35-60 kg was not evaluated, and safety outcomes with this dose are not known. This is particularly important because a relationship between the risk of pancreatitis and the steady state plasma concentration of didanosine was apparent in the original approval trials; dose reduction of Videx was required for pancreatitis and peripheral neuropathy. A more extensive analysis of the didanosine exposures and body weight of the subjects diagnosed with pancreatitis in these early trials was not possible due to unavailability of data. For these reasons, although a possible role of 325 mg/day dose of Videx EC was explored for pediatric patients with BW 35-60 kg, this dose strategy was determined to be unacceptable based on historical Videx dosing and lack of known safety associated with this dose. FDA modification of Applicant's proposed dosing of Videx EC for pediatric patients was further revised as in Table 8.

Table 8: Modification of Applicant's Proposed Dosing Scheme for Videx EC[1]

Body weight (Kg)	Sponsor's Proposed Total Daily Dose	Reviewer's Modified Total Daily Dose
20 to less than 25	200 mg	200 mg
25 to less than 30	(b) (4)	250 mg
30 to less than 60	250 mg	

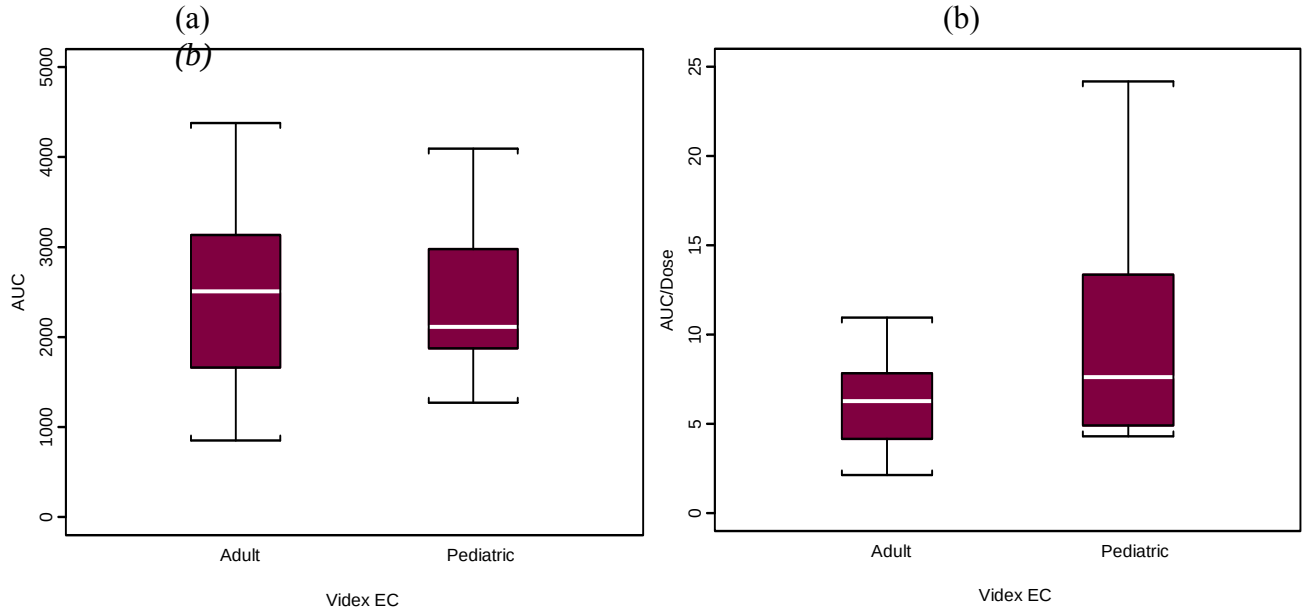
[1]Taking into consideration available results from ACTG116B/117
Source: Clinical Pharmacology Review by Dr. Nitin Mehrotra

5 EFFICACY EVALUATION

The efficacy of Videx EC for treatment of HIV-1 infection in adults was established in 2000. Efficacy in the pediatric population was determined based on extrapolation from adult target efficacy reference; no new efficacy data was submitted in this application. The comparable doses of Videx EC were obtained from BSA-BW conversion using population pharmacokinetic analysis described in Section 4 of this review. The Applicant simulated various BW-based doses of Videx EC in different dose groups to match the adult didanosine exposure. Pharmacokinetic values from Study AI454157, a bioequivalence study of Videx chewable/dispersible buffered tablet and Videx EC capsules, provided a reference range for comparison. Simulations were designed to match the AUC achieved by the simulated pediatric dosing regimens to the adult AUC, and a pediatric dose for a given BW group was considered acceptable if ≥ 75% of subjects could attain the target AUC.

Overall, comparison of adult and pediatric pharmacokinetic parameters revealed overlap of didanosine peak, trough and AUC (Figure 4) among adult and pediatric subjects receiving Videx EC. Although similar results were obtained for both the Applicant's proposed dosing and FDA modified dosing schemes, FDA modified doses resulted in greater magnitude of a favorable shift in the distribution of AUC for 25-35 kg and 35-60 kg weight groups. For reasons described in Section 4, the 325 mg Videx EC dose was deemed unacceptable for 35-60 kg weight group. The antiviral effectiveness of Videx EC in children is thus based on established adult efficacy and is supported by pharmacokinetic data.

Figure 4: Comparison of (a) AUC and (b) dose-normalized AUC of didanosine following administration of Videx EC among adults and pediatrics
Source: Clinical Pharmacology Review for NDA 21-183 SE5-020



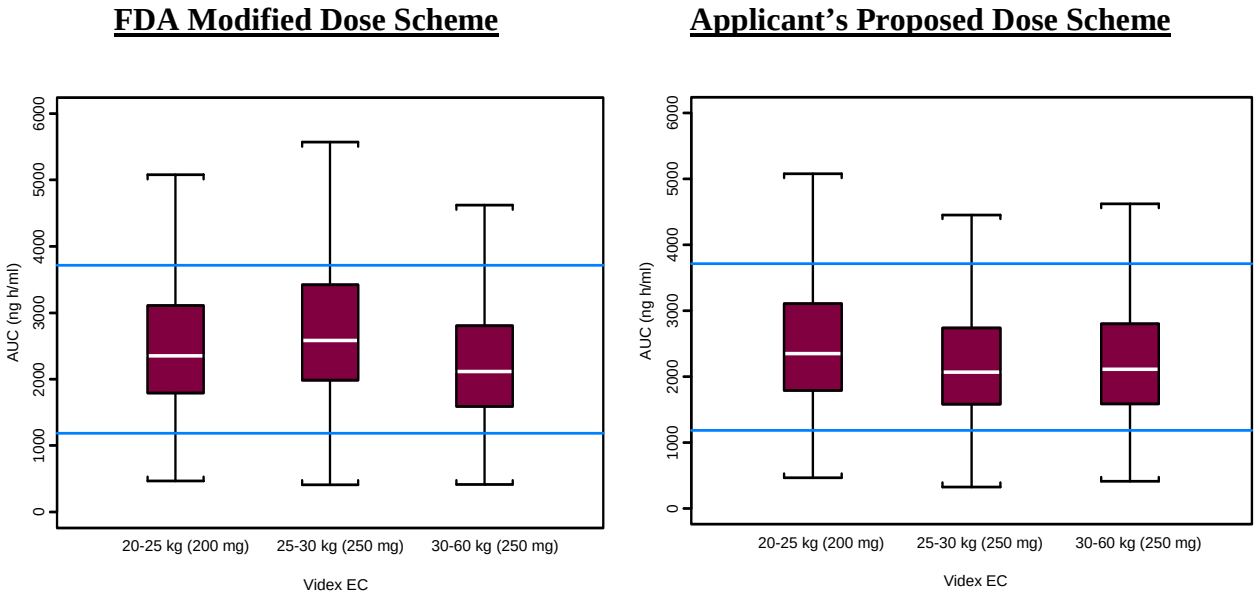
6 SAFETY EVALUATION

6.1 Pediatric Safety

No new safety data was submitted with this sNDA. No new safety issues are anticipated because the proposed pediatric doses will provide drug exposures that fall within the range of exposures observed with the powder formulation in study ACTG152. In this study, conducted in 831 subjects aged 3 months to 18 years, pancreatitis, an adverse event associated with didanosine use in adults patients, resulted in discontinuation of therapy in one subject receiving didanosine and zidovudine. Asymptomatic pancreatic amylase elevation led to changes in treatment in one subject receiving combination of didanosine and zidovudine.

The C_{max} for Videx EC formulation is about 40% lower than the C_{max} observed with the approved Videx buffered powder for pediatric patients. Any deviations in observed exposures remain bracketed within the 10th and 90th percentile of established exposures as shown in Figure 5. Because of these reasons, additional safety concerns with the recommended pediatric dosing are not anticipated.

Figure 5: Evaluation of AUC using Model Based Simulation for 20-25 kg and 25-60 kg Weight Groups
Blue solid lines are the 10th and 90th percentile of AUC obtained in adults receiving EC formulation.
Source: Clinical Pharmacology Review for NDA 21-183 SE5-020



6.2 Special Safety Studies

Hepatic impairment is unlikely to affect didanosine pharmacokinetic profile particularly because this drug is a nucleoside reverse transcriptase inhibitor metabolized by endogenous purine metabolic pathways and excreted primarily via the kidney. The results from a hepatic impairment study, AI454-186, submitted in this sNDA confirmed similar mean plasma concentration-time profiles of didanosine between HIV-negative subjects with and without hepatic impairment. Hence, hepatic impairment does not alter pharmacokinetics of didanosine and dose adjustment is not necessary in individuals with hepatic impairment. Refer to FDA Clinical Pharmacology Review of NDA 21-183 SE5-020 by Dr. Nitin Mehrotra for details.

7 OVERALL ASSESSMENT

7.1 Conclusion

The Applicant and FDA's analyses provide an acceptable comparison of pharmacokinetic exposures of Videx EC between adult and pediatric populations. An appropriate pediatric dosing scheme was derived from meta-analysis of didanosine pharmacokinetics in subjects from seven pediatric and two adult clinical trials. The availability of a once daily preparation of didanosine to children is beneficial because it may enhance medication adherence and provide more convenient dosing compared to larger volumes required for administration of the powder for oral solution. Additionally, this recommendation will provide prescribing physicians the option of calculating didanosine doses based on body weight instead of body surface area; weight based dosing may simplify pediatric dosing in settings with limited resources.

7.2 Recommendation on Regulatory Action

The approval of Videx EC is recommended for the treatment of HIV-1 infection in pediatric patients. This recommendation is based on comparisons based on simulations of Videx EC exposures between pediatric and adult populations. The approval is based on extrapolation of pharmacokinetic exposures of didanosine to approved adult and pediatric dosing of the EC and powder formulations. The following doses of Videx EC are recommended for approval in pediatric patients.

Table 9: Final dose recommendation for Videx EC

Body weight	Dose of Videx EC
20 to less than 25 kg	200 mg of Videx EC once daily
25 to less than 60 kg	250 mg of Videx EC once daily
At least 60 kg	400 mg of Videx EC once daily

7.3 Labeling Review

The proposed Package Insert (PI) and Patient Product Information (PPI) were submitted in Physician's Labeling Rule format. The notable changes proposed by Applicant are summarized below:

1. The indication for Videx EC was expanded to all HIV-infected patients including children in Section 1 of the PI.
2. The dosing recommendation in Section 2.1 was modified to include a pediatric dosing scheme.
3. Pediatric safety and efficacy language was added to Sections 8.4, 12.3 and 14.2. The language related to the design, pharmacokinetics and outcome of pediatric clinical trial ACTG152 are duplicated from the current label for Videx Pediatric Powder for Oral Solution. The following section describing the population pharmacokinetic model and efficacy extrapolation was added in Section 12.3 under Special Populations:

   > The pharmacokinetics of didanosine have been evaluated in HIV-exposed and HIV-infected pediatric patients from birth to adulthood. A population pharmacokinetic analysis was conducted on pooled didanosine plasma concentration data from 9 clinical trials in 106 pediatric (neonate to 18 years of age) and 45 adult patients (greater than 18 years of age). Results showed that body weight is the primary factor associated with oral clearance. Based on the data analyzed, dosing schedule (once versus twice daily) and formulation (powder for oral solution, tablet, and delayed-release capsule) did not have an effect on oral clearance. Didanosine exposure similar to that at recommended adult doses can be achieved in pediatric patients with a weight-based dosing scheme [*see Dosage and Administration (2)*].

4. The results and conclusion from the hepatic impairment study were included in Section 12.3.
5. As per guidelines from the White House Office of National Drug Policy, new language for disposal of unused medicines was incorporated in Section 17.

The FDA recommendations to the proposed PI include the following:

1. Language previously contained in the Black Box pertaining to fatal lactic acidosis reported in pregnant women who have received combination of didanosine and stavudine were re-inserted into the Black Box in the Highlights section of the PI.
2. The Applicant's proposed dosing scheme was modified as discussed in Section 4 of this review and presented in the table below.

FDA Modification of Applicant's Dosing Recommendations for Videx EC

Body weight (Kg)	Sponsor's Proposed Total Daily Dose	FDA Modification Total Daily Dose
20 to less than 25 kg	200 mg	200 mg Videx EC once daily
25 to less than 30kg	(b) (4)	250 mg Videx EC once daily
30 to less than 60 kg	250 mg	

3. Removal of references to (b) (4)

4. Deletion of (b) (4)) (4)

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/s/

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