# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 20-154/S-029, S-030
## 20-155/S-021
## 20-156/S-022

# MEDICAL REVIEW

HFC-530/D. Sullivan

NDA 20-154/SE1-029

DEC 8 1999

**Medical Review**
**(Supplemental NDA)**

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| **Date Submitted:** | **April 29, 1999** |
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**Applicant:** Bristol Myers-Squibb Company
5 Research Parkway
Wallingford, CT 06492



**Drug: Generic** didanosine (ddI)
**Trade** Videx®

**Dosage form:** Chewable/dispersible tablet

**Proposed indication:** Once-daily dosing in the treatment of HIV-1 infection

**Related NDAs:** 20-155 Videx® Buffered powder for oral solution
20-156 Videx® Pediatric powder for oral solution

**Related Documents:** *Submissions dated:* 5/11/99, 5/14/99, 5/18/99, 5/19/99, 6/3/99, 6/24/99, 6/25/99, 7/20/99, 7/21/99, 8/2/99, 8/11/99, 8/12/99, 8/19/99, 8/20/99, 9/2/99, 9/3/99, 9/10,99 9/14/99, 10/13/99, 10/19/99, 10/25/99, 10/26/99, 10/27/99 and 10/28/99.

## 1.0 Resume

The applicant has submitted an application to amend the VIDEX® (didanosine, ddI) label to provide for once-a-day dosing option using a new 200 mg strength reduced mass tablet (2 x 200 mg tablets once daily). To support the new dosage strength and regimen, the applicant has submitted safety, immunologic, and antiviral activity data from three clinical trials. The applicant's rationale for pursuing the once daily dosing option was to provide greater flexibility in the time of ddI dosing, in order to minimize the known interactions of ddI with meals or other drugs.

Study AI454-148 is an ongoing phase 3, open-label, 48-week trial of once daily ddI (2 x 200 mg tablets) in combination with stavudine (d4T)+nelfinavir (NLF) versus the combination of zidovudine (ZDV)+lamivudine (3TC)+NLF in 756 antiretroviral-naïve HIV-1 infected adults. Efficacy results at 24 weeks were similar in both treatment arms. An interim analysis of 387 patients through 24 weeks of treatment demonstrated that the ddI/d4T/NLF and ZDV/3TC/NLF arms produced mean reductions in HIV RNA from baseline of -1.90 and -1.92 $\log_{10}$ copies/mL; mean increases in CD4 cell counts of +164 and +172 cells/$mm^3$; and, 61% and 56% of patients had HIV RNA <400 copies/mL, respectively.

Studies AI454-143 and AI454-146 were 12-week open-label studies that compared ddI(QD)/d4T(BID) to ddI(BID)/d4T(BID) in treatment-naïve HIV-1 infected adult patients. In study 143, the ddI(QD)/d4T regimen produced a -1.59 $\log_{10}$ copies/mL decrease in HIV RNA and a +146 cell/$mm^3$ increase in CD4 cell count, and 41% of patients had HIV RNA levels <400 copies/mL. The ddI(BID)/d4T arm produced similar results: mean reduction from baseline in HIV RNA of -1.65 $\log_{10}$ copies/mL, +135 CD4 cells/$mm^3$, and 39% had HIV RNA levels <400 copies/mL.

In study 146, the 400 mg dose of ddI was administered as 2 x 150 mg + 1 x 100 mg tablets once daily +d4T(BID), and did not utilize the new 200 mg strength reduced mass tablet. The results showed that ddI(QD)+d4T and ddI(BID)+d4T produced -0.9 and -1.1 $\log_{10}$ copies/mL decreases in HIV RNA, +119 and +123 cell/$mm^3$ increases in CD4 cell counts, and 53% and 48% of patients had HIV RNA levels below the limit of quantification of the assay used, <1200 copies/mL, at 12 weeks, respectively.

In study 148, there was one case of fatal pancreatitis occurring in a patient treated with ddI+d4T+NLF. Pancreatitis, fatal and non-fatal, is a well-known serious adverse event associated with ddI when used as monotherapy. During the review of this application, the Division became aware of a number of reports of fatal pancreatitis occurring in patients treated with the combination of ddI+d4T, with and without the addition of hydroxyurea; many of these patients had CD4 cell counts >500 cells/$mm^3$ and were treatment-naïve (see Appendix 1).

Other adverse events, including peripheral neuropathy and elevated liver transaminase and bilirubin levels were clinically significant toxicities associated with ddI and d4T

treatment in the three studies. DDI and d4T have each been associated with these particular adverse events. Thus, the safety review demonstrated that there was evidence for the potential for enhanced risk for these overlapping toxicities when ddI and d4T are used together.

The results from these three studies support amending the ddI label to include once daily dosing of ddI, used in combination with other antiretroviral agents. No data on the activity of once daily ddI for more than 24 weeks was submitted as part of this application. Therefore, it will be important to review the 48-week results of study 148 to determine the durability of the antiviral and immunologic activity of once daily ddI when used as part of a combination regimen; the applicant has agreed to submit these data as a post-approval commitment. The deaths due to pancreatitis raise serious concerns about the safety of the ddI+d4T combination; this potential increased risk for fatal pancreatitis will be emphasized in both the professional and patient label.

## 2.0 Regulatory History

VIDEX was approved in October 1991. In January 1997, the applicant expressed an interest in obtaining an indication for ddI administered on a once daily schedule. The applicant had under development a 200 mg reduced mass tablet strength of ddI that could be administered on a once daily schedule. Because the new 200 mg strength tablet was found not to be bioequivalent to the currently approved tablet strengths, the Division requested data from a clinical study in order to determine if ddI administered once daily would be clinically effective.

In response, the applicant submitted the protocol for study 143, a 12-week comparison of ddI(QD)/d4T(BID) to ddI(BID)/d4T(BID) in treatment-naïve HIV-1 infected adult patients. Concerns that study 143 alone would not provide a sufficient basis to evaluate the equivalence of ddI administered once daily to twice daily because of the short duration of the study and the potential for premature discontinuation due to the dual nucleoside treatment arms, were conveyed to the applicant.

During a November 4, 1997, meeting, the Division and the applicant discussed other potential trial designs for evaluating the efficacy of once daily dosing of ddI. The applicant proposed to conduct study AI454-148 in which ddI once daily+d4T+NLF would be compared to a "standard of care" regimen, such as ZDV+3TC+NLF. The Division and the applicant reached agreement that the proposed study design for study AI454-148 was acceptable.

Although we were concerned that the study did not provide a direct comparison of once to twice daily administration of ddI, we believed it unlikely that the applicant would agree to conduct a 48-week study that specifically evaluated this comparison. However, we concluded that the proposed study could provide interpretable results, for the following reasons:

- The antiviral activity of the ZDV+3TC+NLF regimen is generally understood and predictable in the population studied, treatment-naïve patients. Therefore, if this treatment arm performed as expected, it would provide a basis for assessing whether the once daily ddI-containing regimen was reasonably active; and,

- The antiviral activity of d4T+NLF had also been studied. Therefore, although study 148 was not designed to determine the direct contribution of ddI to the efficacy of the combination, there would be the possibility of observing if the triple combination of ddI+d4T+NLF performed as well or better than the double combination of d4T+NLF.

The protocol for study AI454-146 was not submitted to the Division because this study was not conducted under the US IND.

## 3.0 Study AI454-148

"A Randomized Study of the Long Term Suppression of Plasma HIV RNA Levels by Triple Combination Regimens in Treatment-Naïve Subjects."

The study was initiated in March 1998 and is ongoing. The applicant submitted an interim efficacy analysis of 387 of 756 enrolled patients through 24 weeks of therapy; safety data on the 725 patients who received at least one dose of study medication through June 2, 1999; and, case report forms from patients who died, experienced a serious adverse event or discontinued the study due to an adverse event.

## 3.1 Design

This is a multinational, open-label, 48-week, randomized, phase 3 study designed to compare the antiviral activity and tolerability of ddI dosed once daily in combination with d4T+NLF versus the combination of ZDV+3TC+NLF in HIV-infected antiretroviral-naïve patients with a screening CD4 cell count of at least 100 cells/mm$^3$, and who had a plasma viral load of at least 2,000 HIV RNA copies/mL at entry.

Patients were randomized in a 2:1 ratio to receive ddI once daily (2 x 200 mg tablets)+d4T (40 mg BID)+NLF (750 mg TID). Randomization was stratified according to baseline HIV RNA levels (<30,000 copies/mL and ≥30,000 copies/mL). Treatment will continue for at least 48 weeks after enrollment of the last patients. An interim analysis was planned to occur after approximately one-half of the study population had completed 24 weeks of treatment.

**Comment: Since the study design compares treatment arms that contain two different nucleoside analogues (ddI+d4T compared to ZDV+3TC), it is not possible to distinguish the relative contribution of ddI to efficacy of the combination. The control arm, however, had been studied both in its entirety and its component parts;**

**thus, it was determined that all three agents provided independent contributions to the efficacy of the regimen.**

### 3.2 Patient Population and Disposition

A total of 756 patients were randomized: 503 to ddI+d4T+NLF and 253 to ZDV+3TC+NLF. At entry, 71% of patients were male, 56% were white, 26% were black, and 14% were hispanic. The mean age of study patients was 35 years. Patients entered with a median HIV RNA level of 4.69 $\log_{10}$ copies/mL (range 2.6 to 6.5 $\log_{10}$ copies/mL) and a median CD4 cell count of 340 cells/mm$^3$ (range 80 to 1568 cells/mm$^3$). Seven percent of patients had an AIDS-defining diagnosis at baseline. Thirty-eight percent of patients entered the study with HIV RNA levels <30,000 copies/mL and 62% had HIV RNA ≥30,000 copies/mL.

**Comment: The two arms were similar in baseline demographic and disease characteristics, and represented a population of relatively healthy HIV-infected individuals.**

Of the 756 patients randomized, 725 initiated study medication: 478 in the ddI+d4T+NLF arm and 247 in the ZDV+3TC+NLF arm.

A total of 98 (21%) patient have prematurely discontinued the study from the ddI+d4T+NLF arm and 51 (21%) from the ZDV+3TC+NLF arm. Five patients died (see Section 2.4.1). Thirty-five (7%) and 12 (5%) patients in the ddI+d4T+NLF and ZDV+3TC+NLF arms, respectively, discontinued due to adverse events. The other reasons for discontinuations included loss to follow-up, non-compliance, withdrawal of consent, and treatment failure/disease progression, and these reasons were similarly distributed between the treatment arms.

Eight ddI+d4T+NLF-treated patients had d4T replaced with ZDV because they developed peripheral neuropathy. ZDV was replaced with d4T in 16 patients in the ZDV+3TC+NLF arm, primarily due to gastrointestinal complaints (nausea, vomiting, and/or diarrhea), anemia, or neutropenia.

### 3.3 Results: Efficacy

This study was designed to show that the efficacy of ddI+d4T+NLF regimen was similar to the ZDV+3TC+NLF regimen based on the proportion of patients with week 48 plasma HIV RNA <400 copies/mL (Roche Amplicor HIV-1 Monitor® assay). According to the applicant, 700 patients allocated in a 2:1 manner would provide 90% power to demonstrate similarity between the treatment regimens.

An interim analysis was planned once 350 patients had completed 24 weeks of treatment. The primary endpoint for the interim analysis was the time-averaged difference (TAD) between the two treatment arms in change from baseline HIV RNA levels over the first

24 weeks among patients who had completed 24 weeks of therapy. The applicant also analyzed the proportion of patients with HIV RNA below 400 copies/mL and differences in CD4 cell counts.

**Comment: The analysis of the TAD is not a robust endpoint for assessing equivalence, because it is not a quantifiable variable and represents an average that can minimize differences between treatment regimens. Further, it can be difficult to calculate an average when many patients have low values. Finally, a 0.5 $\log_{10}$ difference is a minimal standard for assessing differences. Proportion below the limit of detection is the agency's preferred analysis, and is more consistent with the goals of treatment.**

The results of the 24 week interim analysis are presented in Table 1.

**Table 1. Efficacy results at week 24**

| | ddI+d4T+NLF | ZDV+3TC+NLF |
|---|---|---|
| Mean change in HIV RNA | -1.90 $\log_{10}$ copies/mL | -1.92 $\log_{10}$ copies/mL |
| HIV RNA <400 copies/mL | 61% | 56% |
| Mean change in CD4s | +164 cells/$mm^3$ | +172 cells/$mm^3$ |

A subgroup analysis of patients with baseline HIV RNA <30,000 copies/mL showed a higher proportion of patients with HIV RNA <400 copies/mL in the ddI+d4T+NLF arm compared to those treated with ZDV+3TC+NLF, 67% and 47%, respectively. For patients who entered with baseline HIV RNA ≥30,000 copies/mL, 57% treated with ddI+d4T+NLF had HIV RNA <400 copies/mL at week 24 and 61% treated with ZDV+3TC+NLF had reached that endpoint.

Five (2%) and two (2%) patients in the ddI+d4T+NLF and ZDV+3TC+NLF arms were diagnosed with an AIDS-defining illness during the first 24 weeks of the study. In the ddI+d4T+NLF arm, candidiasis, herpes simplex, herpes zoster, Kaposi's sarcoma and mycobacterium tuberculosis were the AIDS-defining events. Candidiasis and herpes zoster each accounted for one AIDS-defining event in the ZDV+3TC+NLF arm.

**Comment: The interim analysis showed that the two treatment regimens resulted in a similar proportion of patients with HIV RNA levels <400 copies and similar overall increases in CD4 cell counts through 24 weeks of treatment. In addition, these results were very similar to those found in previous studies of the triple combination of ZDV+3TC+NLF.**

**The HIV RNA response between the two stratums is atypical in that patients in clinical trials of other antiretroviral combinations with baseline HIV RNA ≥30,000 copies/mL generally have higher response rates. Further investigations of these findings are necessary; the week 48 data may be helpful in this respect (please see Statistical Review).**

**There were too few AIDS-defining events at the week 24 analysis to assess the impact of treatment with either regimen on disease progression.**

### 3.4 Safety

The review of safety includes all 725 patients who received study medication from March 6, 1998, the date the first patient was randomized, through June 2, 1999 (median 32 weeks of treatment).

#### 3.4.1 Deaths and Serious Adverse Events

Five deaths have been reported: four from the ddI+d4T+NLF arm and one from the ZDV+3TC+NLF arm. Pancreatitis, Grade 4 peripheral/bulbar neuropathy, respiratory failure, and cardiac arrest following a myocardial infarction were the causes of death in the ddI+d4T+NLF arm. The death due to pancreatitis occurred in a 22-year-old female admitted to the hospital for treatment of acute pancreatitis. Based on review of the CRFs and narratives, this reviewer determined that the deaths due to pancreatitis and neuropathy were related to study medications.

The death in the ZDV+3TC+NLF arm was due to a motor vehicle accident.

Serious adverse events were reported by 8% (n=37) of patients in the ddI+d4T+NLF arm and 6% (n=15) in the ZDV+3TC+NLF arm. In the ddI+d4T+NLF arm, one case of fatal pancreatitis, one death due to Grade IV neuropathy, three Grade 4 lipase elevations, three cases of peripheral neuropathy, one case Grade 4 liver function test elevation, one case of rash, and one case of nausea/vomiting were determined by this reviewer to be related to study medication.

Upper gastrointestinal bleeding resulting in anemia, diabetic ketoacidosis, and elevated liver function tests were assessed by this reviewer to be probably related to study medications in the ZDV+3TC+NLF arm.

**Comment: The death due to pancreatitis in a treatment-naïve patient is of particular concern. Deaths due to pancreatitis in patients treated with the combination of ddI+d4T have been reported recently from clinical trials and post-marketing reports. The ddI label currently contains WARNING information about the potential for fatal pancreatitis; the potential increased risk of fatal pancreatitis when ddI and d4T are used together will be emphasized in the revised label (see Appendix 1).**

**In addition, it appears that patients may be at risk for the overlapping toxicities of peripheral neuropathy and elevated liver function tests when ddI and d4T are used concurrently.**

### 3.4.2 Adverse Events Leading to Study Discontinuation

Overall, 51 patients (10%) have discontinued from the study due to adverse events; 39 (8%) and 12 (5%) from the ddI+d4T+NLF and ZDV+3TC+NLF arms, respectively. Reasons for discontinuation from the ddI+d4T+NLF arm included: peripheral neuropathy (n=13), elevated liver function tests (n=2), elevated lipase levels (n=3), gastrointestinal complaints including nausea, vomiting, diarrhea, abdominal distention/bloating, loss of appetite (n=17), rash (n=3), and, myalgia (n=1). In the ZDV+3TC+NLF arm, gastrointestinal complaints (n=7), rash (n=2), increased liver function tests (n=1), generalized "body pain" (n=1), and depression (n=1) were the events leading to study medication discontinuations.

### 3.4.3 Adverse Clinical and Laboratory Events

Adverse events reported through a median of 32 weeks of study treatment are provided in Table 2.

**Table 2. Selected Clinical Adverse Events, All Grades, N(%)**

| EVENT | DDI+D4T+NLF (N=478) | ZDV+3TC+NLF (N=247) |
|---|---|---|
| Any event | 449 (94) | 227 (92) |
| Diarrhea | 330 (69) | 147 (60) |
| Nausea | 114 (24) | 95 (38) |
| Headache | 94 (20) | 73 (30) |
| Peripheral neuropathy | 108 (23) | 17 (7) |
| Rash | 52 (11) | 32 (13) |
| Vomiting | 38 (8) | 29 (12) |
| Pancreatitis | 1 (<1)* | - |

* Fatal

#### 3.4.3.1 Peripheral Neuropathy

As shown in Table 2, above, peripheral neuropathy occurred significantly more frequently in patients treated with ddI+d4T+NLF (23%) than in patients treated with ZDV+3TC+NLF (7%). Most of the ddI+d4T+NLF-treated patients reported Grade 1 or 2 symptoms. Thirteen patients discontinued study medications, 12 underwent dose reduction or interruption, and eight patients switched from d4T to ZDV due to neuropathic symptoms.

In the ZDV+3TC+NLF arm, no patient reported neuropathy greater than Grade 2 in severity, one patient interrupted therapy, and no patient discontinued or switched study medications due to neuropathy.

**Comment: Peripheral neuropathy is a common adverse event associated with ddI and d4T when used as monotherapies and in combination with each other. The rate of peripheral neuropathy reported in this study is similar to the rate reported in other studies in which patients were treated with ddI and d4T. Although there may be an increased risk for this overlapping toxicity when ddI and d4T are used concurrently, the comparison to ZDV+3TC in this study does not allow evaluations of the potential for additive toxicity.**

### 3.4.3.2 Selected Abnormal Laboratory Tests

The proportions of patients with selected laboratory abnormalities are presented in Table 3.

**Table 3. Selected Laboratory Abnormalities, (%).**

| PARAMETER | ddI+d4T+NLF (N=478) | ZDV+3TC+NLF (N=247) |
|---|---|---|
| SGOT (AST) | | |
| Grade 1-2 | 38 | 20 |
| Grade 3-4 | 2 | 2 |
| SGPT (ALT) | | |
| Grade 1-2 | 34 | 22 |
| Grade 3-4 | 3 | 4 |
| Bilirubin | | |
| Grade 1-2 | 6 | 4 |
| Grade 3-4 | 1 | <1 |
| Lipase | | |
| Grade 1-2 | 11 | 11 |
| Grade 3-4 | 3 | 1 |
| Uric acid | | |
| Grade 1-2 | 9 | 4 |
| Grade 3-4 | 2 | 2 |

**Comment: Grade 1-2 elevations in transaminase and uric acid levels were more common in patients receiving the combination of ddI and d4T. There were more patients treated with ddI and d4T who experienced significantly elevated lipase levels. The rates of these laboratory abnormalities in the ddI+d4T+NLF arm are similar to the rates reported in the current ddI label.**

## 3.5 Summary of Study AI454-148

The data from the interim analysis of this study suggests that the two triple-drug regimens resulted in similar antiviral and immunologic activity through 24 weeks of treatment. Although the relative contribution of ddI to efficacy could not be evaluated, these data support once daily ddI as an acceptable dosing option when used in combination with

other antiretroviral agents. It will be necessary to review the final study data to confirm the durability of these responses.

Fatal pancreatitis, Grade 3-4 elevated lipase levels, peripheral neuropathy, and Grade 1-2 elevated transaminase levels were the most important adverse events related to treatment with ddI+d4T in this study; these events will be reflected in the label.

## 4.0 Study AI454-143

"A Randomized, Double-Blind, Study of the Antiviral Activity of Once-Daily and Twice-Daily Dosing of Didanosine in Combination with Twice-Daily Dosing of Stavudine in HIV-Infected Subjects."

This study was conducted between September 1997 and July 1998 at 21 sites in the United States. The applicant submitted the final study report as well as case report forms from patients who experienced a serious adverse event or discontinued the study due to an adverse event.

### 4.1 Design

This was a randomized, double-blind, 12-week study designed to determine the antiviral activity and tolerability of ddI administered once or twice daily in combination with d4T. HIV-infected patients with CD4 cell counts $\geq$100 cells/mm$^3$, plasma HIV RNA $\geq$10,000 copies/mL, and had not received prior antiretroviral therapy was the population studied. At baseline patients were stratified based on HIV RNA distribution (<30,000 copies/mL and $\geq$30,000 copies/mL).

Patients were randomized to receive ddI 400 mg (2 x 200 mg tablets), once daily+d4T (40 mg) twice daily or ddI 200 mg twice daily+d4T twice daily. Treatment was to continue for 12 weeks after enrollment of the last patient.

### 4.2 Patient Population and Disposition

A total of 100 patients were to be enrolled, 50 per treatment arm. Enrollment was closed prematurely after 88 patients had been randomized because the availability of protease inhibitors made the double nucleoside combinations offered less desirable treatment options.

At baseline, 77% of patients were male; 44% white, 48% black, and 8% hispanic, with a mean age of 35 years. Patients entered with a mean HIV RNA level of 4.65 $\log_{10}$ copies/mL (range 2.6 to 5.6 $\log_{10}$ copies/mL ) and a mean CD4 cell count of 435 cells/mm$^3$ (range 108 to 1083 cells/mm$^3$). Over 70% of patients had asymptomatic HIV disease at baseline.

**Comment: The two arms were similar in their baseline demographic and disease characteristics, and represented a population of relatively healthy HIV-infected individuals.**

During the 12-week treatment period, 16 patients discontinued study medications: nine from the ddI(QD)+d4T arm and seven from the ddI(BID)+d4T arm. The reasons for premature discontinuation from the ddI(QD)+d4T arm included adverse events (n=2), loss to follow-up (n=2), non-compliance (n=2), refusal to continue with therapy (n=2), and one patient went to prison and could no longer receive study medications. In the ddI(BID)+d4T arm, non-compliance (n=1), loss to follow-up (n=3), adverse events (n=2), and change of therapy (addition of a protease inhibitor for high HIV RNA) (n=1) were the reasons for study discontinuation.

After week 12, 25 additional patients discontinued the study. Adverse events (elevated liver function tests, elevated lipase levels, and peripheral neuropathy), loss of response (increased HIV RNA levels), and lost to follow-up were the primary reasons for study discontinuation; these causes were reported with similar frequency between the two treatment arms.

**Comment: The development of adverse events such as neuropathy, elevated lipase levels and liver function tests may occur over time, since there were more study discontinuations for these toxicities after week 12 than prior to week 12.**

### 4.3 Results: Efficacy

The primary objective was to demonstrate that ddI given once daily was as effective as the currently approved twice-daily regimen. The primary endpoint was a comparison of the TAD in HIV RNA between the two regimens over the first 12 weeks of therapy. If the upper limit of the 95% confidence interval for the difference was less than 0.5 $\log_{10}$, the applicant would conclude that the regimens were equivalent. Secondary endpoints included the proportion of patients whose HIV RNA levels were <400 copies/mL (Roche Amplicor® HIV-1 Monitor assay) at week 12, and changes in CD4 cell counts at week 12.

At week 12, the ddI(QD)+d4T regimen produced a mean reduction from baseline in HIV RNA levels of –1.59 $\log_{10}$ copies/mL compared to –1.65 $\log_{10}$ copies/mL for ddI(BID)+d4T.

At week 12, 41% and 39% in the ddI(QD)+d4T and ddI(BID)+d4T arms, respectively, had HIV RNA levels <400 copies/mL, (95% confidence interval –18%, 23%).

The mean increase in CD4 cell counts at week 12 was 146 cells/$mm^3$ for those treated with the QD regimen; those treated with ddI(BID)+d4T had a mean increase of 135 cells/$mm^3$.

There were no differences in HIV RNA or CD4 cell count response between treatment groups based on baseline HIV RNA levels (< or ≥30,000 copies/mL).

**Comment: Although the numbers of patients was small and the confidence intervals were wide, the two dosing regimens appeared to result in similar numeric antiviral responses. There were too few patients remaining in the study beyond week 12 to assess the durability of responses.**

## 4.4 Results: Safety

### 4.4.1 Deaths and Serious Adverse Events

There were no deaths reported during this study.

Serious adverse events were reported by one patient in the ddI(QD)+d4T arm (pneumonia) and six patients in the ddI(BID)+d4T arm (pneumonia, congestive heart failure, depression, tuberculosis, peripheral neuropathy, parotitis, and sialadenitis).

**Comment: A review of the CRFs and narratives did not provide an explanation for the disparity in serious adverse events between the two dosing regimens. However, with the exception of the single case of peripheral neuropathy, these events did not appear to be related to study medications.**

### 4.4.2 Adverse Events Leading to Study Discontinuation

As described in Section 3.2, two patients in each arm discontinued study medication during the first 12 weeks of the study. The two patients who discontinued from the ddI(QD)+d4T arm did so for Grade 3 numbness in the hands and feet (n=1), and Grade 3 elevations of liver function tests with nausea and vomiting (n=1). Grade 4 elevations in liver function tests, and Grade 1 nausea and vomiting accounted for the two discontinuations from the ddI(BID)+d4T arm.

After week 12, two additional patients in the ddI(QD)+d4T arm discontinued treatment due to Grade 3 elevations in liver function tests, and Grade 3 peripheral neuropathy. In the ddI(BID)+d4T arm, four additional patients discontinued after 12 weeks: three due to Grade 2 peripheral neuropathy and one due to Grade 2 fatigue, nausea, vomiting, and elevated liver function tests.

### 4.4.3 Clinical and Laboratory Adverse Events

Adverse events were reported by 77% of ddI(QD)+d4T-treated patients and 91% of ddI(BID)+d4T-treated patients. The types of events reported were similar between the two treatment arms, but for some events the frequency was higher in the ddI(BID)+d4T arm (See Table 4).

**Table 4. Selected Clinical Adverse Events, All Grades, N(%)**

| EVENT | ddI(QD)+d4T (n=44) | ddI(BID)+d4T (n=43) |
|---|---|---|
| Any event | 34 (77) | 39 (91) |
| Diarrhea | 4 (9) | 9 (21) |
| Nausea | 7 (16) | 10 (23) |
| Headache | 7 (16) | 13 (30) |
| Neuropathy | 10 (23) | 11 (26) |
| Rash | 7 (16) | 7 (16) |
| Vomiting | 5 (11) | 3 (7) |
| Pancreatitis | 1 (2) | - |

**Comment: A higher proportion of patients treated with ddI BID experienced diarrhea, nausea and headache; the reasons for the higher rates of these events are unknown.**

The proportions of patients with selected laboratory abnormalities are presented in Table 5.

**Table 5. Selected Laboratory Abnormalities, (%).**

| PARAMETER | ddI(QD)+d4T (n=44) | ddI(BID)+d4T (n=43) |
|---|---|---|
| SGOT (AST) | | |
| Grade 1-2 | 27 | 22 |
| Grade 3-4 | 2 | 10 |
| SGPT (ALT) | | |
| Grade 1-2 | 27 | 22 |
| Grade 3-4 | 5 | 7 |
| Bilirubin | | |
| Grade 1-2 | 15 | 15 |
| Grade 3-4 | 2 | - |
| Lipase | | |
| Grade 1-2 | 12 | 5 |
| Grade 3-4 | 2 | - |
| Uric acid | | |
| Grade 1-2 | - | 2 |
| Grade 3-4 | - | 2 |

**Comment: Grade 1-2 lipase elevations occurred more frequently in patients who received ddI QD. More patients who received ddI BID experienced Grade 3-4 elevations of AST.**

### 4.5 Summary of Study AI454-143

The results of this study demonstrated that the short-term (12-week) antiviral and immunologic activity of 400 mg of ddI administered as 2 of the new 200 mg tablets once-daily plus d4T was similar to 400 mg of ddI administered 200 mg twice-daily using currently approved tablet of ddI with d4T. This was a small equivalence study that failed to achieve the planned enrollment. It was powered based on TAD and not the proportion below detection. This study provides no more than preliminary short-term support for the use of once daily ddI. Finally, the durability of response could not be assessed due to lack of sufficient activity data beyond the 12-week time point.

Elevations of liver function tests and lipase levels, as well as peripheral neuropathy were important toxicities associated with the use of ddI in combination with d4T, and did not appear to be mitigated by once-daily dosing of ddI.

## 5.0 Study AI454-146

"A Randomized Open-Label Study of Virological, Clinical and Safety Effects of a Combination of D4T BID and DDI BID Versus D4T BID and DDI QD in Treatment of HIV-Infected Subjects."

This study was conducted between October 1997, and July 1998, at 17 sites in Italy. The applicant submitted the final study report which included case report forms from patients who experienced serious adverse events and who discontinued the study due to an adverse event.

### 5.1 Design

This was a multi-center, open-label, randomized, 12 week study designed to determine the safety, virologic and clinical effects of the combination of ddI(QD)+d4T versus ddI(BID)+d4T in the treatment of treatment-naïve HIV-infected patients. The primary entry criteria was a CD4 cell count of 200-500 cells/$mm^3$; there were no HIV RNA viral load criteria for entry.

Patients were randomized to receive either ddI 400 mg (2 x 150 mg+1 x 100 mg) once-daily+d4T 40 mg twice daily or ddI 200 mg (2 x 100 mg) twice-daily+d4T 40 mg twice-daily. Treatment was to be continued for three months from the enrollment of the last patient.

### 5.2 Patient Population and Disposition

A total of 120 patients were to be enrolled, 60 per treatment arm. Enrollment was closed after 85 patients had been randomized because of slower than projected enrollment.

At baseline, 67% of patients were male, 98% white, 2% hispanic, with a mean age of 37 years. Patients entered with a mean HIV RNA level of 4.0 $\log_{10}$ copies/mL (46% <10,000 copies/mL and 56% ≥10,000 copies/mL), and a mean CD4 cell count of 388 cells/$mm^3$.

**Comment: The two arms were similar in their baseline demographic and disease characteristics, and represented a population of relatively healthy HIV-infected individuals.**

A total of nine patients discontinued therapy, seven from the ddI(BID)+d4T arm and two from the ddI(QD)+d4T arm. Both patients who discontinued from the ddI(QD)+d4T arm were for loss to follow-up. In the ddI(BID)+d4T arm, subject withdrawal (n=2), loss to follow-up (n=1), adverse events (n=3), and non-compliance (n=1) were the reasons for study discontinuation. All three discontinuations due to adverse events from this arm were for Grade 4 elevations of liver transaminases.

### 5.3 Results: Efficacy

The primary objectives were to demonstrate equivalence of ddI(QD)+d4T and ddI(BID)+d4T, based on antiviral activity, and to assess the safety and tolerance of the two regimens. The primary endpoint compared the TAD between the two regimens in change from baseline $\log_{10}$ in HIV RNA over the first 12 weeks of therapy. If the upper limit of the 95% confidence interval for the difference was less than 0.5 $\log_{10}$, the applicant would conclude that the regimens were equivalent. Secondary endpoints included the proportion of patients with HIV RNA <500 copies/mL (Chiron bDNA assay) and changes in CD4 cell counts.

**Comment: This study utilized an unapproved branched DNA signal amplification assay with a reported lower limit of detection of 500 copies/mL. This assay can not be reliably quantified at levels below 1,200 copies/mL. Further, the units measured by this assay most likely do not represent actual viral particles on an absolute scale and, therefore, do not correlate with other HIV RNA assays. Finally, the applicant did not submit any data to validate that 500 copies/mL was the lower limit of detection, and other studies reviewed by this division have demonstrated that it is not.**

At week 12, the mean change from baseline in HIV RNA for the ddI(QD)+d4T and ddI(BID)+d4T regimens were –0.77 $\log_{10}$ copies/mL and –0.86 $\log_{10}$ copies/mL, respectively.

At week 12, similar proportions of patients had HIV RNA levels <1,200 copies/mL: 53% (23/43) and 48% (20/42) for those treated with ddI(QD)+d4T and ddI(BID)+d4T, respectively.

Patients treated with ddI(QD)+d4T had a mean change in CD4 cell counts at week 12 of 119 cells/mm$^3$, those treated with ddI(BID)+d4T had a mean change of 158 cells/mm$^3$. The difference in CD4 cell count response in the ddI(BID)+d4T arm appeared to be skewed by one patient who had a >800 cell/mm$^3$ increase from baseline within the first two weeks of therapy.

**Comment: The two dosing regimens produced similar short-term immunologic and antiviral activity. There were too few patients remaining in the study beyond week 12 to assess the durability of responses. Also confounding the analysis of long-term outcomes was that after week 12 eight patients in the ddI(QD)+d4T arm initiated therapy with protease inhibitors.**

## 5.4 Results: Safety

### 5.4.1 Deaths and Serious Adverse Events



There were no deaths reported during this study.

Serious adverse events were reported by one patient in the ddI(QD)+d4T arm (neoplasm of the skin) and three patients in the ddI(BID)+d4T arm (fever in two and abdominal pain plus fever in one); based on a review of case report forms none of these events appeared related to study medications.

### 5.4.2 Adverse Events Leading to Study Discontinuation

As described in Section 4.2, three patients in the ddI(BID)+d4T arm discontinued study medications due to Grade 4 elevations of hepatic transaminases (ALT and AST). No patient discontinued therapy due to an adverse event from the ddI(QD)+d4T arm.

### 5.4.3 Clinical and Laboratory Adverse Events

Thirty-three percent (14/43) and 43% (18/42) of patients in the ddI(QD)+d4T and ddI(BID)+d4T arms reported adverse events (see Table 6).

**Table 6. Selected Clinical Adverse Events, All Grades, N(%)**

| EVENT | ddI(QD)+d4T (n=43) | ddI(BID)+d4T (n=42) |
|---|---|---|
| Any event | 14 (33) | 18 (43) |
| Diarrhea | 2 (5) | 4 (10) |
| Nausea | 1 (2) | 5 (12) |
| Headache | - | 4 (10) |
| Neuropathy | - | 1 (2) |
| Rash | 3 (7) | 1 (2) |
| Vomiting | 1 (2) | - |

**Comment: The types of events were consistent with the known adverse event profiles related to treatment with ddI and d4T, but were reported less frequently in this study compared to studies 148 and 143. There are no data to suggest that there were differences in US and non-US patients that would account for the variation in reported adverse events. These variations may be due to differences in reporting practices of adverse events by non-US investigators.**

**Table 7. Selected Laboratory Abnormalities, N(%).**

| PARAMETER | ddI(QD)+d4T (n=43) | ddI(BID)+d4T (n=42) |
|---|---|---|
| SGOT (AST) | | |
| Grade 1-2 | 35 | 46 |
| Grade 3-4 | 7 | 15 |
| SGPT (ALT) | | |
| Grade 1-2 | 47 | 49 |
| Grade 3-4 | 7 | 17 |
| Bilirubin | | |
| Grade 1-2 | 30 | 21 |
| Grade 3-4 | - | - |
| Amylase | | |
| Grade 1-2 | 14 | 10 |
| Grade 3-4 | - | - |
| Uric acid | | |
| Grade 1-2 | - | 2 |
| Grade 3-4 | - | 2 |

**Comment: There was no apparent reduction in the overall risk of laboratory abnormalities with once daily versus twice-daily administration of ddI+d4T.**

### 5.5 Summary of Study AI454-146

Similar to the results of study 143, the results of study 146 demonstrated that the short-term (12-week) antiviral and immunologic activity of 400 mg of ddI administered as 2 x 150 mg + 1 x 100 mg tablets once-per day with d4T was numerically similar to 400 mg of ddI administered as 2 x 100 mg tablets twice-daily with d4T. This was a small equivalence study that failed to achieve the planned enrollment. It was powered based on TAD and not on the proportion below detection. This study provides preliminary short-term support for using ddI once daily. Also, the durability of response could not be assessed due to lack of sufficient activity data beyond the 12-week time point. Finally, this study did not utilize the new 200 mg strength tablet, so its overall contribution to an assessment of safety and efficacy for the proposed new formulation could not be established.

Elevations in liver function tests and amylase levels were the most important toxicities identified in this study, and did not appear to be mitigated by once daily administration of ddI.

## 6.0 Overall Summary of Efficacy and Safety

Three clinical trials, AI454-143, 146 and 148 were submitted by the applicant to support amending the ddI label to provide for once daily administration of ddI and a new dosage strength (200 mg reduced mass tablet).

The 24 week analysis of study 148 showed that ddI administered once daily ddI+d4T+NLF produced similar short-term antiviral and immunologic activity as ZDV+3TC+NLF. Because of the multiple substitutions it was not possible to determine the direct contribution of ddI to efficacy

Studies 143 and 146 were two small 12 week studies comparing the antiviral and immunologic activity of ddI administered once or twice daily in combination with d4T. The results of these trials do not contradict the short-term findings of study 148; however, each study lacks sufficient power to draw firm conclusions.

The results of study 148 are sufficiently robust to support the conclusion that once daily administration of ddI is a safe and effective option when ddI is used as a component of combination therapy for the treatment of patients with HIV infection.

Pancreatitis is an established adverse event associated with the monotherapy use of ddI. Recently, there has been a significant increase in the use of ddI+d4T alone, or in combination with other antiretroviral agents, including hydroxyurea. During review of this application, the Division has become aware of a number of cases of fatal pancreatitis in patients treated with these combinations (see Appendix 1). Since the applicant has been promoting the ddI+d4T combination, with hydroxyurea, as safe and effective, it is imperative that patients and clinicians be fully informed about the potential increased risks for the overlapping toxicities of pancreatitis (fatal and non-fatal), peripheral neuropathy, and elevations in liver function tests.

## 7.0 Labeling

The label submitted by the applicant included a detailed description of Study 148, revisions to the Dosage and Administration describing once-daily administration and the Adverse Events section. The label also included proposed revisions to the Overdose section to warn clinicians about the risk of phenyalanine overdose with the administration of more than two ddI tablets at any one time.

Because of concerns about the deaths due to pancreatitis in patients treated with ddI+d4T, with and without hydroxyurea, the professional and patient labels needed to address the potential increased risk of this toxicity when these agents are administered concurrently.

In addition, the division revised the Carcinogencity/Mutagenicity section of the draft labeling to bring it up-to-date. Finally, the division requested that the applicant provide additional precautionary statements related to the need for patients to receive at least two ddI tablets at each dose (to ensure adequate buffering) and not to exceed four tablets at each dose (to reduce the risk of GI side effects.)

Both the patient and professional label submitted by the sponsor on October 28, 1999, adequately addressed the division's concerns and was acceptable. The sponsor also agreed to distribute Dear Healthcare professional and Dear Investigator letters at the time this supplement is approved to further emphasize the risk of pancreatitis.

## 8.0 Phase IV Commitments

- The applicant will provide the final report of study AI454-148, as soon as it is available.
- The applicant will submit proposals to provide data to support once daily dosing as well as use of the 200 mg strength tablet of ddI in pediatric patients.
- The applicant will submit a comprehensive risk assessment of fatal and non-fatal pancreatitis in patients treated with ddI alone and in combination with d4T with and without hydroxyurea.

## 9.0 Recommended Regulatory Action

Based on a review of the data submitted, this supplement should be approved. The label will reflect the potential for fatal pancreatitis in patients treated with ddI+d4T, with and without hydroxyurea, as well as the potential for other overlapping toxicities of peripheral neuropathy and elevated liver function tests.

/S/

Russell Fleischer, PA-C, MPH
Senior Clinical Analyst

APPEARS THIS WAY
ON ORIGINAL

**Concurrence:**
HFD-530/DivDir/HJolson /S/ 12/8/99
HFD-530/TLMO/TCvetkovic /S/ 12/7/99

**CC:**
HFD-530/DepDir/DBirnkrant
HFD-530/NDAs 20-154, 20-155, 20-164

HFD-530/Division File
HFD-725/Stats/GSoon/GAras
HFD-530/Micro/LMishra/LConnors
HFD-530/BioPharm/RKumi/KReynolds
HFD-530/Chem/KLo/SMiller
HFD-530/PharmTox/ABigger/JFarrelly
HFD-530/PM/DSillivan
HFD-530/MO/RFleischer



APPEARS THIS WAY
ON ORIGINAL

## APPENDIX 1

Pancreatitis is an established adverse event associated with the monotherapy use of ddI. Since its approval in 1991, the ddI label has carried a warning about fatal and nonfatal pancreatitis. This warning was based on the incidence of pancreatitis found in Phase III trials in patients with very advanced HIV disease that ranged from 1% to 10% with doses higher than are currently recommended and 1% to 7% with recommended dose. There are now deaths due to pancreatitis that have been reported from clinical trials studying the combination of ddI+d4T, with and without hydroxyurea, in patients who were treatment-naïve and treatment-experienced without significant immunosuppression, and at the recommended doses of ddI and d4T. In addition, deaths due to pancreatitis occurring in patients treated with the combination of ddI and d4T, with and without hydroxyurea, have been reported to the MedWatch program. The following summarizes these cases:

- **ACTG 5025**

During the review of this supplement, the Division was notified on September 2, 1999, of two deaths due to pancreatitis that had occurred in a NIH Division of AIDS study, ACTG 5025. ACTG 5025 was a randomized study designed to determine if switching patients with documented viral suppression while receiving indinavir (IDV), ZDV, and 3TC to a regimen of IDV, ddI, and d4T with or without hydroxyurea (HU) prolongs viral suppression. Both deaths occurred in patients treated with IDV 800 mg Q8h+ddI 400 mg QD+d4T 40 mg BID+HU 600 mg BID; there were 68 patients in this arm at the time the deaths were reported.

- The first death occurred in a 49-year-old male. The patient was hospitalized in March 1999, for pancreatitis approximately four months after initiation of study medications; study medications were stopped. A CT scan of the abdomen revealed a pancreatic pseudocyst with ascites. The patient developed sepsis and disseminated intravascular coagulation and died. The patient's HIV RNA level was 880,000 copies/mL within one week of stopping study medications, CD4 cell count was not reported.

- The second death occurred in a 51-year-old male. In March 1999, the patient began to complain of abdominal pain and was admitted to hospital with a diagnosis of pancreatitis. On April 15, the patient developed gram negative sepsis, anuria, acidosis and hypotension; he died that same day. The patient's CD4 cell count and HIV RNA were not reported.

On September 22, the Division was notified that the DSMB recommended termination of ACTG 5025 because of toxicity in the ddI+d4T+HU+IDV arm of the study. A letter to study investigators informing them about the termination of the study was issued by DAIDS on September 24, 1999.

- **BMS Submitted Cases**

On September 3, 1999, DAVDP requested the applicant provide data from clinical trials and post-marketing reports on all deaths in patients treated with ddI plus d4T with or without HU; this information was submitted on September 10, and consisted primarily of MedWatch forms. There were 21 deaths reported due to pancreatitis or complications related to pancreatitis. A review of the limited information provided by the applicant yielded the following:

- Two deaths from study ACTG 5025 and one death from study AI454-148, reviewed above.

- A 64-year-old male treated with ddI+d4T+HU+nevirapine was hospitalized for jaundice, nausea, vomiting, anorexia and shortness of breath. The cause of death was reported as lactic acidosis with steatosis, severe fungal infection and disseminated intravascular coagulation. At the time of death, the patient had elevated lipase (value not reported) and amylase (246 U/L).

- A 27-year-old male treated with ddI+d4T+IDV was hospitalized for treatment of pancreatitis. He became tachycardic, tachypneic, acidotic and died of circulatory shock. At the time of death, the lipase was >4,000 U/L.

- A 60-year-old male treated with ddI+d4T+NLF+efavirenz was hospitalized complaining of abdominal pain and vomiting. His lipase was >14,000 U/L and amylase was 4,755 U/L. He progressed to renal failure and died.

- A 45-year-old male treated with ddI+d4T+NLF was hospitalized for necrotizing pancreatitis. Immediately following a CT scan, the patient developed acute renal failure and adult respiratory distress syndrome and died.

- A 43-year-old female treated with ddI+d4T+efavirenz was hospitalized for necrotizing pancreatitis. The cause of death was reported as disseminated intravascular coagulation.

- A 42 year-old male treated with ddI+d4T was hospitalized for liver failure and pancreatitis. The cause of death was reported as acute liver failure, hypoglycemia and increased ammonia consistent with Reye's syndrome.

- Two patients treated with ddI+d4T, unknown age, sex or clinical course.

- A 38-year-old male treated with d4T+nevirapine was hospitalized for abdominal pain diagnosed as gastritis. A CT scan showed hepatosplenomgealy and a normal pancreas. The cause of death was reported as pancreatitis.

- A 40-year-old female treated with ddI+d4T+NLF was hospitalized for a one week history of abdominal pain and vomiting. The lipase was >28,000 U/L and the amylase was 770 U/L. The cause of death was reported as respiratory failure secondary to lactic acidosis.

- A 45 year-old male treated with ddI+d4T+NLF+nevirapine was hospitalized for abdominal pain that started approximately one week following the addition of 3TC to the treatment regimen. The patient died one week later due to pancreatitis.

- A 37 year-old male treated with ddI+d4T was admitted to the hospital for abdominal pain and vomiting. A diagnosis of pancreatitis was made. The cause of death was reported as kidney failure and lactic acidosis.

- A 3 year-old female treated with ddI+d4T reportedly died of pancreatitis. At the time of death the amylase and lipase levels were elevated (values not reported).

- A 42 year-old male treated with ddI+d4T who died due to microvesicular hepatocellular steatosis; pancreatitis was noted on autopsy.

- A 29 year-old female treated with ddI+d4T+efavirenz+invirase was hospitalized for a one week history of abdominal pain. The cause of death was reported as necrotizing pancreatitis. At the time of death the amylase was 300 U/L.

- An unknown aged male treated with ddI+d4T+NLF was hospitalized for peripheral neuropathy and acute urinary retention. The patient developed pancreatitis and died.

- A 31 year-old female treated with ddI+d4T+Norvir was hospitalized for acute abdominal pain. Norvir was switched to NLF. The patient underwent an appendectomy. At surgery, a hematoma in the retroperitoneum was noted and thought to be secondary to colonoscopy. The patient developed pancreatitis with an amylase of 2,475 U/L and died.

- A 38 year-old male treated with ddI+d4T+NLF+nevirapine hospitalized for a three week history of nausea and vomiting. The cause of death was reported as staphyloccocus aureus and klebsiella pneumoniae sepsis. At the time of death, the lipase was 500,000 U/L and amylase was 1521 U/L.

- **Cases from Other Sources**

In September 1999, a death in a 34 year-old male treated with ddI+d4T+nevirapine due to lactic acidosis, pancreatitis and multiple organ failure was reported by another pharmaceutical manufacturer through the MedWatch system; no further information was available.

- **Division of Risk Evaluation Consult**

The Division of Risk Evaluation of the Center for Drug Evaluation and Research was asked to review reports of pancreatitis associated with ddI when used as monotherapy and in combination with other nucleoside reverse transcriptase inhibitors (NRTIs), with particular attention to the combination of ddI+d4T (see attachment 1). The salient findings of this consult include:

- The percentage of deaths in patients receiving NRTI combination with ddI was 36% in 1997, 42% in 1998, and 35% in 1999. Nearly all of these reports, 90%, involved stavudine.

- Four of the 25 patients who died between 1998-1999 were receiving concomitant hydroxyurea.

- Thirteen patients died between 1998-1999 due lactic acidosis, acidosis, and/or fatty liver. In these cases, elevated amylase/lipase levels and/or pancreatitis were noted at the time of death.

- There has been a significant increase in ddI and d4T use starting in 1997 and 1996, respectively. For example, in 1998, there were approximately [redacted] prescriptions written for ddI. Sixty percent of the time that ddI was prescribed, d4T was prescribed as a concomitant medication. Unfortunately, it is not possible to determine if pancreatitis is solely due to ddI or if the concomitant use of d4T is somehow promoting pancreatitis.

**Assessment**

There have been a worrisome number of deaths in patients treated with ddI+d4T, with and without hydroxyurea, due directly to pancreatitis or as a component of another clinical syndrome (e.g., lactic acidosis). Many of these cases have occurred in treatment-naïve patients and patients who are treatment-experienced but who have reasonably intact immune systems. The data provided was, in many cases, sparse and there did not appear to be aggressive follow-up of these cases by the applicant. For example, in most cases no CD4 cell count, treatment status, concomitant medications, or the full clinical course was provided or fully described. In addition, pancreatitis is a labeled adverse events associated with ddI, so it is likely that there has been significant underreporting of this toxicity to the sponsor and the FDA MedWatch program. Also, because the total number of patients treated with the specific combination of ddI+d4T is unknown, a true assessment of risk of death due to pancreatitis cannot be made. However, since the applicant has been promoting ddI+d4T, with hydroxyurea, as a safe and effective combination, patients and clinicians should be adequately informed of the potential risk for this serious complication.