DIDANOSINE

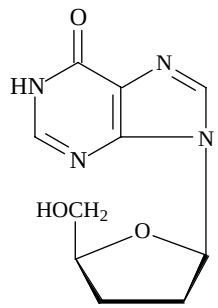
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 69655-05-6
Chem. Abstr. Name: 2′,3′-Dideoxyinosine
IUPAC Systematic Name: 2′,3′-Dideoxyinosine
Synonyms: ddI; DDI; dideoxyinosine

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{10}H_{12}N_4O_3$ Relative molecular mass: 236.23

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White, nonhygroscopic crystalline powder (American Hospital Formulary Service, 1997)
(*b*) *Melting-point*: 160–163 °C (Budavari, 1996)
(*c*) *Spectroscopy data*: Infrared, ultraviolet, nuclear magnetic resonance (proton and ^{13}C) and mass spectral data have been reported (Nassar *et al*., 1993).
(*d*) *Solubility*: Soluble in water (27.3 mg/mL at 25 °C and pH 6.2); soluble in dimethylsulfoxide; slightly soluble in ethanol and methanol; insoluble in chloroform (National Cancer Institute, 1992; Nassar *et al.*, 1993; American Hospital Formulary Service, 1997)

(*e*) *Stability*: Stable at neutral or slightly alkaline pH, but unstable at acidic pH. At pH less than 3, complete hydrolysis to hypoxanthine and 2′,3′-dideoxyribose occurs in less than 2 min at 27 °C (American Hospital Formulary Service, 1997)

(*f*) *Dissociation constant*: pK_a, 9.13 (American Hospital Formulary Service, 1997)

(*g*) *Optical rotation*: $[\alpha]_D^{20}$, –25.7 ± 2° (National Cancer Institute, 1992)

1.1.4 *Technical products and impurities*

Didanosine is available as a 25-, 50-, 100- and 150-mg chewable, dispersible buffered tablet, a 100-, 167-, 250- and 375-mg buffered powder for oral solution and a 2- and 4-g unbuffered paediatric powder for oral solution. The tablets may also contain aspartame, calcium carbonate, dihydroxyaluminium sodium carbonate, flavours (mandarin orange, wintergreen), magnesium hydroxide, magnesium stearate, microcrystalline cellulose, phenylalanine, polyplasdone, silicon dioxide, sodium citrate, sorbitol and sucrose. The buffered powder for oral solution is buffered with a citrate–phosphate buffer (composed of dibasic sodium phosphate, sodium citrate and citric acid) and sucrose (Gennaro, 1995; American Hospital Formulary Service, 1997; Canadian Pharmaceutical Association, 1997; Bristol-Myers Squibb Co., 1998; British Medical Association/Royal Pharmaceutical Society of Great Britain, 1998; Editions du Vidal, 1998; LINFO Läkemedelsinformation AB, 1998; Rote Liste Sekretariat, 1998; Thomas, 1998; US Pharmacopeial Convention, 1998).

Trade names for didanosine include DDI Filaxis, Megavir, Ronvir and Videx (Swiss Pharmaceutical Society, 1999).

1.1.5 *Analysis*

Several reverse-phase high-performance liquid chromatography (HPLC) methods have been reported for the determination of didanosine and its impurities or degradates in bulk drug substance or formulations. HPLC procedures also have been developed for the analysis of didanosine and its major metabolite, hypoxanthine, in biological fluids, including plasma, urine and cerebrospinal fluid (Nassar *et al*., 1993).

1.2 Production

2′,3′-Dideoxynucleosides are typically synthesized from 2′-deoxynucleosides by Barton-type deoxygenation reactions or from intact nucleosides by several steps involving deoxygenation reactions to 2′,3′-unsaturated deoxynucleosides, which are then hydrogenated. Approaches through ketonucleosides and a photoreductive process have also been described (Nassar *et al*., 1993).

Selective benzoylation of the 5′-hydroxyl group of 2′-deoxyinosine is achieved by dropwise addition of a pyridine solution of benzoyl chloride to 2′-deoxyinosine suspended in pyridine. The 5′-*O*-benzoyl-2′-deoxyinosine formed is then treated in one portion with 1,1′-thiocarbonyldiimidazole to form the thioimidazolide. Deoxygenation at the 3′ position of the thioimidazolide gives 5′-*O*-benzoyl-2′,3′-dideoxyinosine. Removal of the benzoate group by treatment with anhydrous methanol saturated with anhydrous ammonia at 0 °C yields didanosine in 90% yield (Nassar *et al.*, 1993).

Didanosine has also been prepared enzymatically by deamination of 2′,3′-dideoxyadenosine with adenosine deaminase at room temperature. Recrystallization from methanol gave an 85% yield (Nassar *et al.*, 1993).

Information available in 1999 indicated that didanosine was manufactured and/or formulated in 26 countries (CIS Information Services, 1998; Swiss Pharmaceutical Society, 1999).

1.3 Use

Didanosine is a nucleoside analogue and a highly potent nucleoside reverse transcriptase inhibitor, which has been used in the treatment of human immunodeficiency virus (HIV) infections since 1990 (Lambert *et al.*, 1990). It is among the most durable agents in this class (i.e. viral resistance develops most slowly) (Kahn *et al.*, 1992; Spruance *et al.*, 1994; Dolin *et al.*, 1995; Hammer *et al.*, 1996; Englund *et al.*, 1997), although resistance does eventually develop (Kozal *et al.*, 1994). It has been extensively studied both as a single therapy and in combinations, especially with zidovudine (see monograph, this volume) and didehydrodideoxythymidine (stavudine) (Montaner *et al.*, 1998; Raffi *et al.*, 1998); combinations are more effective than monotherapy (McKinney *et al.*, 1998).

The major drawback of the agent in its current formulation is that its acid lability requires administration on an empty stomach with a substantial quantity of antacid, which can lead to gastrointestinal intolerance (Pike & Nicaise, 1993; American Hospital Formulary Service, 1997). An enteric coated form, which still must be taken on an empty stomach but does not contain antacids, is being developed.

The rare development of pancreatitis (which can be severe) and peripheral neuropathy limited use of this agent in initial therapy in the past (Pike & Nicaise, 1993). It is currently being prescribed for once-daily administration (Cooley *et al.*, 1990), and in combination with hydroxyurea to potentiate its antiviral effect (see the monograph on hydroxyurea, this volume).

Like most nucleoside analogues, didanosine is excreted primarily in the kidney, and the dose should probably be modified for patients with renal dysfunction (Singlas *et al.*, 1992; Knupp *et al.*, 1996).

1.4 Occurrence

Didanosine is not known to occur as a natural product. No data on occupational exposure were available to the Working Group.

1.5 Regulations and guidelines

Didanosine is not listed in any international pharmacopoeias.

2. Studies of Cancer in Humans

Pluda *et al.* (1993) examined the records of 61 patients with AIDS or severe AIDS-related complex (defined as having either oral candidiasis, oral hairy leukoplakia or weight loss of > 10% of total body weight) who were entered into a phase I study of didanosine and 2′,3′-dideoxyadenosine during 1988–89. 2′,3′-Dideoxyadenosine is rapidly converted to didanosine after its administration. All patients had fewer than 350 CD4 cells/μL plasma at the time of entry. They were treated and followed for a maximum of 3.7 years, during which time four (6.6%) developed a non-Hodgkin lymphoma, all of which were characterized as high-grade B-cell tumours. The estimated cumulative risk of all 61 patients of developing non-Hodgkin lymphoma by 24 months of therapy was 6.2% (95% confidence interval [CI], 2.1–17%, Kaplan-Meier method), increasing to 9.5% (3.6–23%) by 36 months. [The Working Group noted that the cumulative risks are difficult to interpret in the absence of a suitable reference group consisting of AIDS patients with a similar degree of immunosuppression.]

In a multicentre trial in the USA, Abrams *et al*. (1994) randomly assigned 467 symptomatic HIV-infected patients with CD4 counts of ≤ 300 cells/μL plasma who had previously received zidovudine to treatment with either didanosine at 500 mg per day (n = 230) or zalcitabine at 2.25 mg per day (n = 237). The patients were recruited during 1990–91 and were treated and followed up for a median of 1.3 years and a maximum of 1.8 years. Three cases of non-Hodgkin lymphoma was seen in the didanosine-treated group and six in the zalcitabine-treated group. [The Working Group noted that rate ratios were not calculated, although the risk ratio for non-Hodgkin lymphoma in patients treated with didanosine compared with that in the patients receiving zalcitabine was 0.5 (95% CI, 0.13–2.0), with no adjustment for differences in survival between the two groups.]

In an international randomized trial, the Delta Coordinating Committee (1996) allocated 3207 individuals with antibodies to HIV, symptoms of infection or a CD4 count of 350 cells/μL plasma to treatment with either zidovudine at 600 mg per day (n = 1055), zidovudine plus didanosine at 400 mg per day (n = 1080) or zidovudine plus zalcitabine at 2.25 mg per day (n = 1072). The patients were treated and followed up for a median of 2.5 years (range, 1.8–2.9), during which time 14 deaths due to cancer

[not further specified] occurred; five of the deaths occurred in the group treated with zidovudine alone, five in the group treated with zidovudine plus didanosine and four in the group treated with zalcitabine.

[The Working Group noted that these trials were designed to compare the efficacy of drugs in the treatment of patients with various degrees of severity of immunosuppression. For the purposes of evaluating cancer risk, therefore, the numbers of participants were too small and the length of follow-up too short, cancer incidence may have been underascertained, and cancer rates could not be analysed adequately.]

3. Studies of Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The pharmacokinetics of didanosine has been reviewed and summarized extensively (Hartman *et al*., 1990; Yarchoan *et al*., 1990a; Knupp *et al*., 1991; Faulds & Brogden, 1992; Perry & Balfour, 1996; Beach, 1998). The pharmacokinetics is linear over a broad dose range (0.4–16.5 mg/kg bw) and is similar after a single initial oral dose and after weeks of oral dosing (Knupp *et al*., 1991). Drug disposition can be slowed significantly, however, in patients with compromised renal function (Burger *et al*., 1995; Perry & Balfour, 1996). The peak concentration in plasma ranges between 2.2 and 11.8 μmol/L (0.52–2.8 mg/L) for doses between 125 and 375 mg and is reached after 30–60 min (Hartman *et al*., 1990; Burger *et al*., 1995; Perry & Balfour, 1996). The half-time for removal of the drug from plasma is approximately 1 h (Hartman *et al*., 1990; Knupp *et al*., 1991; Faulds & Brogden, 1992; Perry & Balfour, 1996). The total body clearance rate after oral administration has been reported to be 20–60 L/h, and the renal clearance is somewhat slower, about 20–30 L/h (Hartman *et al*., 1990; Knupp *et al*., 1991; Faulds & Brogden, 1992; Perry & Balfour, 1996; Beach, 1998). The pharmacokinetics of didanosine is not significantly altered when it is administered with zidovudine (Morse *et al*., 1995; Sahai *et al*., 1995).

A single oral dose of 375 mg didanosine was administered to two pregnant women (length of amenorrhoea, 21 and 24 weeks). Maternal blood was collected by venepuncture, and amniotic fluid and fetal blood samples were taken 65 and 78 min after

treatment. Didanosine crossed the placenta, with fetal:maternal ratios of 0.14 and 0.19 (Pons *et al*., 1991).

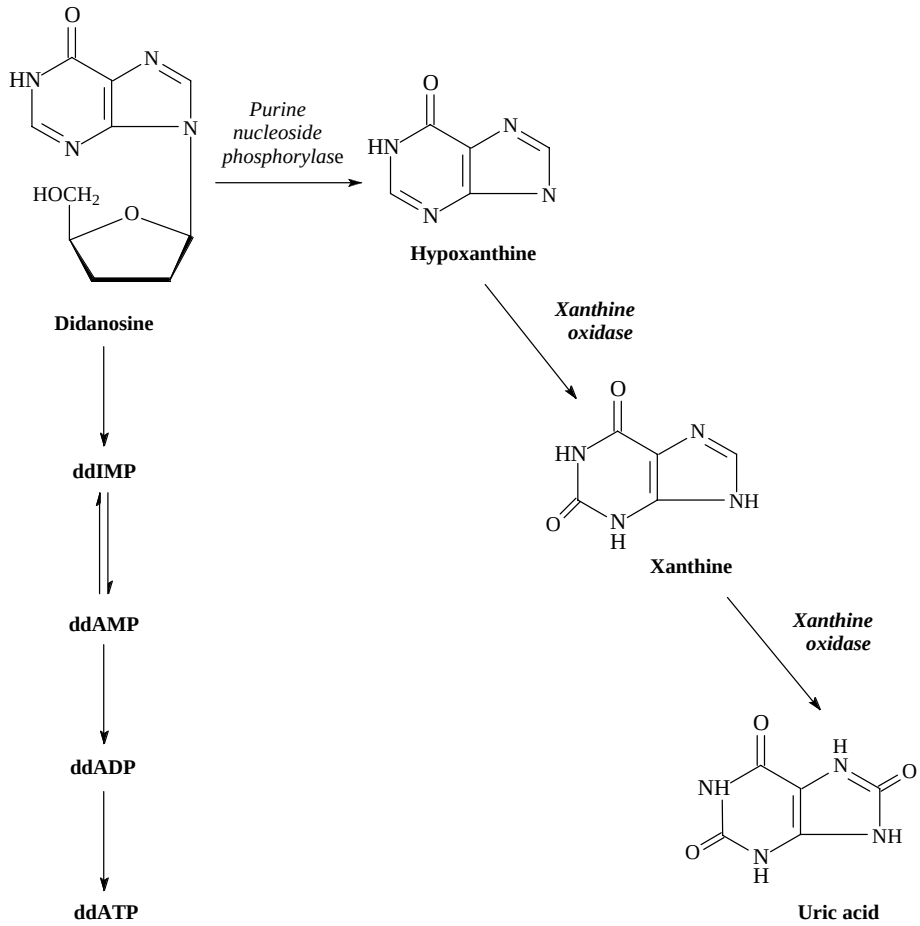
Single, isolated portions (cotyledons) of fresh, full-term human placenta were perfused from both the fetal and the maternal side with Krebs-Ringer buffer (closed or open system). The transfer of didanosine (3–30 μmol/L) across the placenta was reported to be passive, with equal transfer in both directions. Little or no placental metabolism of didanosine was reported (Dalton & Au, 1993; Henderson *et al*., 1994).

Single, isolated cotyledons of fresh, full-term placenta were perfused from both the fetal and the maternal side with Earle's buffered salt solution with added glucose, amino acids and serum albumin (concentration of didanosine, 1–500 μmol/L). Neither perfusate was recirculated. HPLC of the maternal outflow indicated that 25% of the didanosine was metabolized, whereas about 50% of that in the fetal perfusate was metabolized. No didanosine triphosphate was detected in the placenta (Dancis *et al*., 1993).

The absorption, distribution, metabolism and excretion of didanosine in adults with and without HIV infection have been reviewed extensively (Yarchoan *et al*., 1990a; Faulds & Brogden, 1992; Burger *et al*., 1995; Perry & Balfour, 1996; Beach, 1998). Most of these studies and the use of the drug in clinical practice involve oral dosing at 400 mg/day, although intravenous dosing was documented in a number of studies (Perry & Balfour, 1996). Oral dosing poses specific problems because the drug is acid-labile and its bioavailability decreases in the presence of food (Hartman *et al*., 1991). When didanosine is given with antacid at doses of 0.8–10.2 mg/kg bw per day to fasting patients, its bioavailability is 35–40% (Yarchoan *et al*., 1990a; Hartman *et al*., 1991; Knupp *et al*., 1991; Perry & Balfour, 1996), and its entry into cells is thought to occur by passive diffusion (Faulds & Brogden, 1992). Didanosine is poorly bound to plasma proteins (≤ 5%) (Burger *et al*., 1995; Perry & Balfour, 1996) and is apparently less widely distributed than zidovudine because it is less lipophilic (Perry & Balfour, 1996). It is, however, distributed to plasma and cerebrospinal fluid, the concentrations in the latter typically being much lower than those in plasma (Hartman *et al*., 1990; Yarchoan *et al*., 1990a; Perry & Balfour, 1996; Beach, 1998).

Didanosine is metabolized along two pathways (Figure 1). A quantitatively minor pathway that is responsible for the antiretroviral activity of the drug involves phosphorylation and reversible amination of didanosine monophosphate to dideoxyadenosine monophosphate through the action of adenylosuccinate synthetase and adenylosuccinate lyase (Yarchoan *et al*., 1990a; Back *et al*., 1992; Faulds & Brogden, 1992). The dideoxyadenosine monophosphate is further phosphorylated to the triphosphate (ddATP) by purine nucleoside monophosphate kinase and purine nucleoside diphosphate kinase. The intracellular half-time of ddATP is 12–24 h, suggesting that less frequent dosing may be required than with zidovudine or zalcitabine (Yarchoan *et al*., 1990a). In addition to inhibiting the viral reverse transcriptase, ddATP becomes incorporated into DNA and terminates the replicating DNA chain in both cellular and viral DNA (Faulds & Brogden, 1992). Although dideoxyadenosine phosphorylation is

Figure 1. Metabolic pathways of didanosine



From Back *et al.* (1992)
ddIMP, didanosine 5′-monophosphate; ddAMP, 2′,3′-dideoxyadenosine 5′-monophosphate; ddADP, 2′3′-dideoxyadenosine 5′-diphosphate; ddATP, 2′3′-dideoxyadenoxine 5′-triphosphate

critical to the mechanism of antiviral activity, it is responsible for only a small fraction of the total drug disposition. Approximately 40% of the total dose is recovered as unchanged drug in the urine, about 50% as hypoxanthine and about 4% as uric acid (Yarchoan *et al*., 1990a; Faulds & Brogden, 1992; Burger *et al*., 1995; Perry & Balfour, 1996; Beach, 1998), while non-renal clearance occurs via metabolism and/or biliary excretion (Back *et al*., 1992; Burger *et al*., 1995). The major metabolic pathway (Figure 1) involves metabolism to uric acid through purine nucleotide phosphorylase, which produces hypoxanthine. This compound either re-enters the purine nucleotide pools or is further metabolized to xanthine and uric acid through the action of xanthine oxidase (Hartman *et al*., 1990; Back *et al*., 1992; Burger *et al*., 1995).

4.1.2 *Experimental systems*

The pharmacokinetics of didanosine in monkeys is somewhat similar to that in humans (Qian *et al*., 1991; Ravasco *et al*., 1992; Hawkins *et al*., 1995). The time to maximum plasma concentration was 30 min (Ravasco *et al*., 1992), and the half-time for removal of the drug from plasma varied between 1.2 and 1.8 h (Qian *et al*., 1991; Ravasco *et al*., 1992; Hawkins *et al*., 1995). The plasma clearance rate ranged from 9.6 to 16.7 mL/min per kg bw (Qian *et al*., 1991; Ravasco *et al*., 1992; Hawkins *et al*., 1995), while the renal clearance was reported to be 2 mL/min per kg bw (Ravasco *et al*., 1992). The proportion of the drug excreted unchanged in the urine was reported to be either 19% (Qian *et al*., 1991) or 74% (Ravasco *et al*., 1992). There is evidence of extensive distribution in the body, although the concentration in cerebrospinal fluid was 4.8% of that observed in plasma (Hawkins *et al*., 1995).

In rats, didanosine is distributed to the plasma, kidney, brain, cerebrospinal fluid and intestine after oral or intravenous dosing at 40–200 mg/kg bw (Hoesterey *et al*., 1991; Wientjes & Au, 1992a,b; Bramer *et al*., 1993; Hasegawa *et al*., 1996). Bioavailability of 14–33% has been reported after oral and rectal administration (Wientjes & Au, 1992a,b; Bramer *et al*., 1993; Hasegawa *et al*., 1996); intestinal absorption was reduced by digestive tract acidity (Hasegawa *et al*., 1996). The rate of clearance of the drug from plasma was 66–115 mL/min per kg bw, while the renal clearance rate in the same rats was 18–33 mL/min per kg bw (Wientjes & Au, 1992a,b). The time from dosing to maximum plasma concentration was reported to be 8–35 min (Hoesterey *et al*., 1991; Wientjes & Au, 1992a; Bramer *et al*, 1993), and the half-time for removal from plasma was 24–38 min (Hoesterey *et al*., 1991; Wientjes & Au, 1992a,b). Unchanged drug in the urine accounted for 4% of the total dose after several hours (Wientjes & Au, 1992a) and 18% in a 24-h urine collection (Bramer *et al*., 1993). The clearance rates appear to slow with increasing dose, and the biphasic decline in plasma concentrations after dosing was suggestive of a slow equilibrium with tissue. The concentrations of drug in the brain and cerebrospinal fluid reached 5% and 2%, respectively, of those in plasma (Hoesterey *et al*., 1991). Clearance of didanosine from the brain and cerebral spinal fluid is retarded by probenecid (Hoesterey *et al*, 1991). The pharmacokinetics does not change in the presence of zidovudine (Wientjes & Au, 1992b).

In dogs, didanosine given orally or intravenously at doses of 20–500 mg/kg bw was metabolized rapidly, and 46–51% of the dose was recovered in urine; the other 50% was unaccounted for. The rate of clearance from plasma was 23 mL/min per kg bw, and the half-time for removal was 30–60 min (Kaul *et al*., 1991; Wientjes *et al*., 1991). The concentrations in cerebrospinal fluid were 3–11% of those in plasma (Wientjes *et al*., 1991).

Three pregnant rhesus monkeys (*Macaca mulatta*) that were near term (146 days) received radiolabelled didanosine as a bolus dose of 2.0 mg/kg bw into the radial vein. During a 3-h sampling period of both the mothers and the fetuses, the fetal:maternal ratio

of the integrated area under the curve of plasma concentration–time was 0.33 ± 0.08 at 3 h, and fetal tissues contained 0.2–4 μmol/L didanosine (Sandberg *et al*., 1995)

4.2 Toxic effects

4.2.1 *Humans*

Didanosine is toxic primarily to the nervous system, inducing peripheral neuropathy and headache; the gastrointestinal system, inducing pancreatitis and hepatitis; and the haematological system, inducing leukopenia (Yarchoan *et al*., 1990a,b; Pike & Nicaise, 1993; Beach, 1998). In an early study (Rozencweig *et al*., 1990) of 92 patients treated with didanosine, 12 experienced neuropathy, nine had liver enzyme abnormalities, four had myelosuppression, three had pancreatitis, and two had skin rash. Later studies suggested that didanosine has a weaker association with peripheral neuropathy than was suggested in phase I clinical trials (Kelleher *et al*., 1999). Peripheral neuropathy has been observed mainly at high doses and in individuals treated for at least four months. The effect has been demonstrated in 12–34% of didanosine-treated patients, and is reversible upon withdrawal of the drug (Rozencweig *et al*., 1990; Yarchoan *et al*., 1990b; Simpson & Tagliati, 1995; Kelleher *et al.*, 1999).

Acute pancreatitis was reported by Maxson *et al*. (1992) in 12 of 51 patients during about eight months of follow-up after the start of didanosine therapy. In a second study (Seidlin *et al*., 1992), seven of 44 patients developed pancreatitis lasting from one to seven weeks and varying in severity from mild to life-threatening. Among 7806 zidovudine-resistant patients participating in the Didanosine Expanded Access Program, 5% reported pancreatitis (Pike & Nicaise, 1993). In all of the studies, the symptoms correlated with cumulative treatment and typically subsided after discontinuation of therapy.

Like zidovudine and zalcitabine, didanosine occasionally caused a rare (1 in 10^5 to 1 in 10^6 patients) idiosyncratic syndrome consisting of increased liver enzyme activity, hepatic steatosis, fulminant hepatitis and severe lactic acidosis after long-term (more than three months) treatment; this syndrome can be fatal (Lai *et al*., 1991; Bissuel *et al*., 1994; Hu & French, 1997). Other miscellaneous and rare human toxic effects include acute, reversible thrombocytopenia (Lor & Liu, 1993), retinal toxicity (Cobo *et al*., 1996), nephrotoxicity (Crowther *et al*., 1993) and widespread cutaneous eruption, possibly associated with malignancies and infections (Just *et al*., 1997).

4.2.2 *Experimental systems*

Most of the studies of the toxicity of didanosine in animal models have addressed immune competence (Phillips & Munson, 1997; Phillips *et al*., 1997), neurotoxicity (Warner *et al*., 1995; Schmued *et al*., 1996) and pancreatic toxicity (Grady *et al*., 1992; Nordback *et al*., 1992).

In $B6C3F_1$ mice given didanosine by gastric intubation at 100, 250, 500 or 1000 mg/kg bw per day for 14, 28 or 180 days, virtually no toxic effects were seen in specific organs, with the exception of spleen and thymus (Phillips & Munson, 1997; Phillips *et al*., 1997). Cell-mediated (T cell) immunity was moderately suppressed at 250 mg/kg bw for > 14 days, and suppression of humoral (B cell) immune response was observed at 100 mg/kg bw given for > 28 days.

In order to investigate the mechanism of didanosine-induced neuropathy, rats were dosed orally twice daily with 41.5 or 415 mg/kg bw didanosine in a phosphate buffer vehicle. Myelin splitting and intramyelin oedema were observed in the sciatic nerves of treated animals in a dose-related fashion (Schmued *et al*., 1996). In rabbits given 750 or 1500 mg/kg bw didanosine per day for 6 or 16 weeks, no evidence of peripheral neuropathy was found (Warner *et al*., 1995).

Attempts to model the effects of didanosine in the human pancreas have been unsuccessful. Grady *et al*. (1992) gave male Wistar rats didanosine at 100 or 1400 mg/kg bw per day for about one month and found no alterations in pancreatic morphology, lysozymal cathepsin B activity or amylase secretion. Nordback *et al*. (1992) perfused the pancreas of dogs with 500 μmol/L didanosine for 4 h and found that the oxygen consumption and protein secretion decreased, but these changes did not mimic the typical response seen in human pancreatitis.

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups of 5–15 pregnant CD1 mice were given didanosine subcutaneously at 10, 30, 100 or 300 mg/kg bw per day throughout gestation. No changes in the numbers of resorptions or pups per litter or in external embryo morphology were reported in animals examined on gestational day 11. The pups of treated dams were born live, developed at a normal rate and had a normal lifespan (Sieh *et al.*, 1992).

Human embryonic or fetal cells (6–11 weeks of development) exposed to didanosine at 10 mmol/L were reported to contain less protein than control cells [data not shown as mean ± SD]. Cells prepared from 11-day CD1 mouse embryos were treated in culture with didanosine at concentrations of 1 μmol/L to 10 mmol/L. Concentrations > 5 mmol/L decreased the protein content. No selective cytotoxicity was seen in neuronal, cardiac or skeletal muscle or cartilage cells (Sieh *et al*., 1992).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Reports on the potential mutagenicity of didanosine are sparse. References such as *The Physician's Desk Reference* (Medical Economics Data Production, 1999) provide results but few or no details of the experimental conditions used in the assays. The manufacturer of the drug has yet to publish a detailed report equivalent to those available in the literature on aciclovir and zidovudine. Mutagenicity was seen *in vitro* and *in vivo* only with high doses of didanosine (Table 1).

Didanosine did not induce reverse mutation in *Salmonella typhimurium* with or without exogenous metabolic activation [no information on doses or strains] and did not induce differential toxicity in *Escherichia coli* or *Bacillus subtilis*.

Didanosine marginally increased the number of revertants in *E. coli* WP2 *uvr*A. Mamber *et al*. (1990) assessed the ability of didanosine to induce two SOS functions, cell filamentation and prophage lambda, in *E. coli*. The combined results of tests for the induction of the SOS response in the nucleoside analogues evaluated in this volume indicate that the activity relationships can be ranked zidovudine > didanosine > zalcitabine. The results indicate that didanosine does not cause DNA damage that requires repair involving the excision repair (*uvr*A) or error-free postreplication repair (*rec*A) processes. Rather, didanosine, which acts as a DNA chain terminator, may generate an SOS-inducing response leading to inhibition of DNA replication. Didanosine caused clastogenic effects in Chinese hamster ovary cells and human lymphocytes.

Studies of the mutagenicity of didanosine in animals *in vivo* are limited to assays for micronucleus formation in rodents. Phillips *et al*. (1991) administered didanosine to mice by gavage for three days or 13 weeks (five days per week) and found no increase in micronuclei even at extremely high doses. As didanosine can be inactivated by the low pH of the stomach, it was subsequently administered by intraperitoneal injection for three consecutive days. A significant clastogenic response was found in peripheral blood at the low and high doses.

Concomitant exposure of human lymphoblastoid TK6 cells to equimolar concentrations of didanosine and zidovudine potentiated the mutagenic responses at both the *HPRT* and *TK* loci. Over a range of concentrations, the induced mutant frequencies at the two loci were three to four times greater than the values obtained after exposure to didanosine or zidovudine alone. In addition, the levels of DNA incorporation of zidovudine in cells exposed to the combination of drugs was about twofold greater than those measured in cells exposed to analogous concentrations of zidovudine alone (Meng *et al.*, 2000) (see section 4.4.2 in the monograph on zidovudine).

Table 1. Genetic and related effects of didanosine

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium [strains not reported], reverse mutation	–	–	NR	Medical Economics Data Production (1999)
Escherichia coli BR513 (*uvr*B *env*A *lac*Z*::lambda*), prophage induction, SOS repair (spot and liquid suspension tests)	+	NT	50	Mamber *et al*. (1990)
Escherichia coli PQ37 (*uvr*A *rfa lac*Z*::sul*A), cell filamentation, SOS repair (spot and liquid suspension tests)	+	NT	[X]	Mamber *et al*. (1990)
Escherichia coli WP2 *uvr*A, reverse mutation	(+)	(+)	NR	Medical Economics Data Production (1999)
Escherichia coli CM871 (*uvr*A *rec*A *lex*A), differential toxicity (vs *Escherichia coli* WP2)	–	NT	1000	Mamber *et al*. (1990)
Bacilllus subtilis M45 *rec* strain, differential toxicity	–	NT	NR	Mamber *et al*. (1990)
Bacilllus subtilis H17, gene mutation	–	NT	NR	Mamber *et al*. (1990)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	(+)	(+)	2000	Medical Economics Data Production (1999)
Chromosomal aberrations, Chinese hamster cells *in vitro*	+	NT	500	Medical Economics Data Production (1999)
Cell transformation, BALB/c 3T3 mouse cells	+	NT	3000	Medical Economics Data Production (1999)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	500	Medical Economics Data Production (1999)
Micronucleus formation, mouse cells *in vivo*	–		NR	Medical Economics Data Production (1999)
Micronucleus formation, mouse bone-marrow cells *in vivo*	–		3000 po × 3	Phillips *et al*. (1991)
Micronucleus formation, mouse peripheral blood cells *in vivo*	–		1000 po × 5; 13 wk	Phillips *et al*. (1991)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, mouse peripheral blood cells *in vivo*	+		200 ip × 5; 13 wk	Phillips *et al*. (1991)
Micronucleus formation, mouse bone-marrow cells *in vivo*	–		108 ip × 1	Motimaya *et al*. (1994)
Micronucleus formation, rat cells *in vivo*	–		NR	Medical Economics Data Production (1999)

[a] +, positive; (+), weak positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day; NR, not reported; po, orally; ip, intraperitoneally; wk, week; [X] indicated in figure but not clearly specified

4.5 Mechanistic considerations

The main mechanism of the toxicity and antiviral efficacy of didanosine appears to be related to its phosphorylation and subsequent incorporation into DNA (Brinkman *et al*., 1998; Peter & Gambertoglio, 1998). The monophosphate is converted to dideoxyadenosine monophosphate, which is further phosphorylated before incorporation into DNA (Yarchoan *et al.*, 1990a). Once incorporated, the absence of a 3′-hydroxy group on the ribose of the dideoxyadenosine molecule prevents extension of the replicating DNA chain (Brinkman *et al*., 1998). The antiviral activity of dideoxyadenosine triphosphate is thought to result both from direct inhibition of the viral reverse transcriptase and from truncation of proviral DNA replication (Yarchoan *et al.*, 1990a; Brinkman *et al*., 1998; Peter & Gambertoglio, 1998).

Like other nucleoside analogue drugs, didanosine, which is converted to dideoxyadenosine, can become incorporated into mitochondrial DNA and truncate its replication (Chen *et al*., 1991), impairing the oxidative phosphorylation capacity of the cell and depleting mitochondrial DNA (Youssef & Badr, 1992; Lewis & Dalakas, 1995; Benbrik *et al.*, 1997; Brinkman *et al*., 1998).

The few available studies on the mutagenicity of didanosine show that it produces primarily clastogenic effects at high doses. This activity is consistent with its action as a DNA chain terminator.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Didanosine is a nucleoside analogue which has been used since approximately 1990 in the treatment of HIV infection in adults and children. It is in widespread use in combination regimens with other antiretroviral agents, and potentiation of the antiviral effect of didanosine by hydroxyurea is being investigated.

5.2 Human carcinogenicity data

The only data available were from three trials designed to assess the efficacy of didanosine in improving the degree of immunocompetence and survival of patients with HIV infection, and no conclusion could be drawn about carcinogenicity.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

The human pharmacokinetics of orally administered didanosine is linear over a broad range of doses. Didanosine is about 40% bioavailable. It is rapidly absorbed, distributed and eliminated. About half of the human urinary metabolites are represented by hypoxanthine, and 40% is unchanged drug. Phosphorylation is a minor pathway but is essential for the antiviral activity of the drug.

The toxic effects of didanosine in humans include peripheral neuropathy, pancreatitis, hepatitis and leukopenia.

No relevant studies of the reproductive and prenatal effects of didanosine in humans were available. Didanosine crosses the placenta of women and monkeys by bidirectional, passive diffusion. Didanosine but not didanosine triphosphate was observed in placental and fetal tissues.

Little information was available on the genetic and related effects of didanosine. Didanosine was mutagenic *in vitro* and *in vivo* only at high doses. Treatment of human cells in culture significantly increased the mutant frequencies after short-term exposure to concentrations 10–20-fold greater than the peak plasma concentrations found in some patients. In the same studies, didanosine was more cytotoxic and less mutagenic than zidovudine.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of didanosine.

There is *inadequate evidence* in experimental animals for the carcinogenicity of didanosine.

Overall evaluation

Didanosine is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

Abrams, D.I., Goldman, A.I., Launer, C., Korvick, J.A., Neaton, J.D., Crane, L.R., Grodesky, M., Wakefield, S., Muth, K., Kornegay, S., Cohn, D.L., Harris, A., Luskin-Hawk, R., Markowitz, N., Sampson, J.H., Thompson, M., Deyton, L. & the Terry Beirn Community Programs for Clinical Research on AIDS (1994) A comparative trial of didanosine or zalcitabine after treatment with zidovudine in patients with human immunodeficiency virus infection. *New Engl. J. Med.*, **330**, 657–662

American Hospital Formulary Service (1997) *AHFS Drug Information® 97*, Bethesda, MD, American Society of Health-System Pharmacists, pp. 456–465

Back, D.J., Ormesher, S., Tjia, J.F. & Macleod, R. (1992) Metabolism of 2′,3′-dideoxyinosine (ddI) in human blood. *Br. J. clin. Pharmacol*., **33**, 319–322

Beach, J.W. (1998) Chemotherapeutic agents for human immunodeficiency virus infection: Mechanism of action, pharmacokinetics, metabolism, and adverse reactions. *Clin. Ther*., **20**, 2–25

Benbrik, E., Chariot, P., Bonavaud, S., Ammi-Saïd, M., Frisdal, E., Rey, C., Gherardi, R. & Barlovatz-Meimon, G. (1997) Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. *J. neurol. Sci*., **149**, 19–25

Bissuel, F., Bruneel, F., Habersetzer, F., Chassard, D., Cotte, L., Chevallier, M., Bernuau, J., Lucet, J.-C. & Trepo, C. (1994) Fulminant hepatitis with severe lactate acidosis in HIV-infected patients on didanosine therapy. *J. intern. Med*., **235**, 367–372

Bramer, S.L., Wientjes, M.G. & Au, J.L.-S. (1993) Absorption of 2′,3′-dideoxyinosine from lower gastrointestinal tract in rats and kinetic evidence of different absorption rates in colon and rectum. *Pharm. Res*., **10**, 763–770

Brinkman, K., ter Hofstede, H.J.M., Burger, D.M., Smeitink, J.A.M. & Koopmans, P.P. (1998) Adverse effects of reverse transcriptase inhibitors: Mitochondrial toxicity as common pathway. *AIDS*, **12**, 1735–1744

Bristol-Myers Squibb Co. (1998) *Package Insert: Videx® (Didanosine)*, Princeton, NJ

British Medical Association/Royal Pharmaceutical Society of Great Britain (1998) *British National Formulary*, No. 36, London, p. 277

Budavari, S., ed. (1996) *The Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., p. 524

Burger, D.M., Meenhorst, P.L. & Beijnen, J.H. (1995) Concise overview of the clinical pharmacokinetics of dideoxynucleoside antiretroviral agents. *Pharm. World Sci*., **17**, 25–30

Canadian Pharmaceutical Association (1997) *CPS Compendium of Pharmaceuticals and Specialties*, 32nd Ed., Ottawa, pp. 1710–1713

Chen, C.-H., Vazquez-Padua, M. & Cheng, Y.-C. (1991) Effect of anti-human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. *Mol. Pharmacol*., **39**, 625–628

CIS Information Services (1998) *Worldwide Bulk Drug Users Directory 1997/98 Edition*, Dallas, TX [CD-ROM]

Cobo, J., Ruiz, M.F., Figueroa, M.S., Antela, A., Quereda, C., Pérez-Elías, M.J., Corral, I. & Guerrero, A. (1996) Renal toxicity associated with didanosine in HIV-infected adults. *AIDS*, **10**, 1297–1299

Cooley, T.P., Kunches, L.M., Saunders, C.A., Ritter, J.K., Perkins, C.J., McLaren, C., McCaffrey, R.P. & Liebman, H.A. (1990) Once-daily administration of 2′,3′-dideoxyinosine (ddI) in patients with the acquired immunodeficiency syndrome or AIDS-related complex. *New Engl. J. Med.*, **322**, 1340–1345

Crowther, M.A., Callaghan, W., Hodsman, A.B. & Mackie, I.D. (1993) Dideoxyinosine-associated nephrotoxicity. *AIDS*, **7**, 131–132

Dalton, J.T. & Au, J.L.-S. (1993) 2′,3′-Dideoxyinosine is not metabolized in human placenta. *Drug Metab. Dispos.*, **21**, 544–546

Dancis, J., Lee, J.D., Mendoza, S. & Liebes, L. (1993) Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J. acquir. Immune Defic. Syndr*., **6**, 2–6

Delta Coordinating Committee (1996) Delta: A randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet*, **348**, 283–291

Dolin, R., Amato, D.A., Fischl, M.A., Pettinelli, C., Beltangady, M., Liou, S.-H., Brown, M.J., Cross, A.P., Hirsch, M.S., Hardy, W.D., Mildvan, D., Blair, D.C., Powderly, W.G., Para, M.F., Fife, K.H., Steigbigel, R.T., Smaldone, L. & the AIDS Clinical Trials Group (1995) Zidovudine compared with didanosine in patients with advanced HIV type 1 infection and little or no previous experience with zidovudine. *Arch. intern. Med.*, **155**, 961–974

Editions du Vidal (1998) *Dictionnaire Vidal 1998*, 74th Ed., Paris, OVP, pp. 1967–1970

Englund, J.A., Baker, C.J., Raskino, C., McKinney, R.E., Petrie, B., Fowler, M.G., Pearson, D., Gershon, A., McSherry, G.D., Abrams, E.J., Schliozberg, J. & Sullivan, J.L. (1997) Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. *New Engl. J. Med*., **336**, 1704–1712

Faulds, D. & Brogden, R.N. (1992) Didanosine. A review of its antiviral activity, pharmacokinetic properties and therapeutic potential in human immunodeficiency virus infection. *Drugs*, **44**, 94–116

Gennaro, A.R. (1995) *Remington: The Science and Practice of Pharmacy*, 19th Ed., Easton, PA, Mack Publishing Co., Vol. II, p. 1333

Grady, T., Saluja, A.K., Steer, M.L., Lerch, M.M., Modlin, I.M. & Powers, R.E. (1992) *In vivo* and *in vitro* effects of azidothymidine analog dideoxyinosine on the exocrine pancreas of the rat. *J. Pharmacol. exp. Ther*., **262**, 445–449

Hammer, S.M., Katzenstein, D.A., Hughes, M.D., Gundacker, H., Schooley, R.T., Haubrich, R.H., Henry, W.K., Lederman, M.M., Phair, J.P., Niu, M., Hirsch, M.S. & Merigan, T.C. for the AIDS Clinical Trials Group Study 175 Study Team (1996) A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell countrs from 200 to 500 per cubic millimeter. *New Engl. J. Med.*, **335**, 1081–1090

Hartman, N.R., Yarchoan, R., Pluda, J.M., Thomas, R.V., Marczyk, K.S., Broder, S. & Johns, D.G. (1990) Pharmacokinetics of 2′,3′-dideoxyadenosine and 2′,3′-dideoxyinosine in patients with severe human immunodeficiency virus infection. *Clin. Pharmacol. Ther*., **47**, 647–654

Hartman, N.R., Yarchoan, R., Pluda, J.M., Thomas, R.V., Wyvill, K.M., Flora, K.P., Broder, S. & Johns, D.G. (1991) Pharmacokinetics of 2′,3′-dideoxyinosine in patients with severe human immunodeficiency infection. II. The effects of different oral formulations and the presence of other medications. *Clin. Pharmacol. Ther*., **50**, 278–285

Hasegawa, T., Juni, K., Saneyoshi, M. & Kawaguchi, T. (1996) Intestinal absorption and first-pass elimination of 2′,3′-dideoxynucleosides following oral administration in rats. *Biol. pharm. Bull*., **19**, 599–603

Hawkins, M.E., Mitsuya, H., McCully, C.M., Godwin, K.S., Murakami, K., Poplack, D.G. & Balis, F.M. (1995) Pharmacokinetics of dideoxypurine nucleoside analogs in plasma and cerebrospinal fluid of rhesus monkeys. *Antimicrob. Agents Chemother*., **39**, 1259–1264

Henderson, G.I., Perez, A.B., Yang, Y., Hamby, R.L., Schenden, R.S. & Schenker, S. (1994) Transfer of dideoxyinosine across the human isolated placenta. *Br. J. clin. Pharmacol*., **38**, 237–242

Hoesterey, B.L., Galinsky. R.E. & Anderson, B.D. (1991) Dose dependence in the plasma pharmacokinetics and uptake kinetics of 2′,3′-dideoxyinosine into brain and cerebrospinal fluid of rats. *Drug Metab. Dispos.*, **19**, 907–912

Hu, B. & French, S.W. (1997) 2′,3′-Dideoxyinosine-induced Mallory bodies in patients with HIV. *Am. J. clin. Pathol.*, **108**, 280–283

Just, M., Carrascosa, J.M., Ribera, M., Bielsa, I. & Ferrándiz, C. (1997) Dideoxyinosine-associated Ofuji papuloerythroderma in an HIV-infected patient. *Dermatology*, **195**, 410–411

Kahn, J.O., Lagakos, S.W., Richman, D.D., Cross, A., Pettinelli, C., Liou, S.-H., Brown, M., Volberding, P.A., Crumpacker, C.S., Beall, G., Sacks, H.S., Merigan, T.C., Beltangady, M., Smaldone, L., Dolin, R. & the NIAID AIDS Clinical Trials Group (1992) A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *New Engl. J. Med.*, **327**, 581–587

Kaul, S., Knupp, C.A., Dandekar, K.A., Pittman, K.A. & Barbhaiya, R.H. (1991) Pharmacokinetics of 2′,3′-dideoxyinosine (BMY-40900), a new anti-human immunodeficiency virus agent, after administration of single intravenous doses to beagle dogs. *Antimicrob. Agents Chemother.*, **35**, 610–614

Kelleher, T., Cross, A. & Dunkle, L. (1999) Relation of peripheral neuropathy to HIV treatment in four randomized clinical trials including didanosine. *Clin. Ther.*, **21**, 1182–1192

Knupp, C.A., Shyu, W.C., Dolin, R., Valentine, F.T., McLaren, C., Martin, R.R., Pittman, K.A. & Barbhaiya, R.H. (1991) Pharmacokinetics of didanosine in patients with acquired immunodeficiency syndrome or acquired immunodeficiency syndrome- related complex. *Clin. Pharmacol. Ther.*, **49**, 523–535

Knupp, C.A., Hak, L.J., Coakley, D.F., Falk, R.J., Wagner, B.E., Raasch, R.H., van der Horst, C.M., Kaul, S., Barbhaiya, R.H. & Dukes, G.E. (1996) Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: Influence of hemodialysis and continuous ambulatory peritoneal dialysis. *Clin. Pharmacol. Ther.*, **60**, 535–542

Kozal, M.J., Kroodsma, K., Winters, M.A., Shafer, R.W., Efron, B., Katzenstein, D.A. & Merigan, T.C. (1994) Didanosine resistance in HIV-infected patients switched from zidovudine to didanosine monotherapy. *Ann. intern. Med.*, **121**, 263–268

Lai, K.K., Gang, D.L., Zawacki, J.K. & Cooley, T.P. (1991) Fulminant hepatic failure associated with 2′,3′-dideoxyinosine (ddI). *Ann. intern. Med.*, **115**, 283–284

Lambert, J.S., Seidlin, M., Reichman, R.C., Plank, C.S., Laverty, M., Morse, G.D., Knupp, C., McLaren, C., Pettinelli, C., Valentine, F.T. & Dolin, R. (1990) 2′,3′-Dideoxyinosine (ddI) in patients with the acquired immunodeficiency syndrome or AIDS-related complex. A phase I trial. *New Engl. J. Med.*, **322**, 1333–1340

Lewis, W. & Dalakas, M.C. (1995) Mitochondrial toxicity of antiviral drugs. *Nature Med.*, **1**, 417–422

LINFO Läkemedelsinformation AB (1998) *FASS 1998 Läkemedel i Sverige*, Stockholm, pp. 1243–1244

Lor, E. & Liu, Y.Q. (1993) Didanosine-associated eosinophilia with acute thrombocytopenia. *Ann. Pharmacother.*, **27**, 23–25

Mamber, S.W., Brookshire, K.W. & Forenza, S. (1990) Induction of the SOS response in *Escherichia coli* by azidothymidine and dideoxynucleotides. *Antimicrob. Agents Chemother.*, **34**, 1237–1243

Maxson, C.J., Greenfield, S.M. & Turner, J.L. (1992) Acute pancreatitis as a common complication of 2′,3′-dideoxyinosine therapy in the acquired immunodeficiency syndrome. *Am. J. Gastroenterol.*, **87**, 708–713

McKinney, R.E., Jr, Johnson, G.M., Stanley, K., Yong, F.H., Keller, A., O'Donnell, K.J., Brouwers, P., Mitchell, W.G., Yogev, R., Wara, D.W., Wiznia, A., Mofenson, L., McNamara, J. & Spector, S.A. (1998) A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J. Pediatr.*, **133**, 500–508

Medical Economics Data Production (1999) *PDR®: Physicians' Desk Reference*, 53rd Ed., Montvale, NJ

Meng, Q., Olivero, O.A., Shi, X., Walker, D.W., Antiochos, B., Poirier, M.C. & Walker, V.E. (2000) Enhanced DNA incorporation of AZT and synergistic effects of AZT and DDI in inducing *HPRT* and *TK* mutations in human cells (abstract). *Environ. mol. Mutag.*, **35** (Suppl. 31), 43

Montaner, J.S.G., Reiss, P., Cooper, D., Vella, S., Harris, M., Conway, B., Wainberg, M.A., Smith, D., Robinson, P., Hall, D., Myers, M. & Lange, J.M.A. (1998) A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients. The INCAS Trial. *J. Am. med. Assoc.*, **279**, 930–937

Morse, G.D., Shelton, M.J., Ho, M., Bartos, L., DeRemer, M. & Ragni, M. (1995) Pharmacokinetics of zidovudine and didanosine during combination therapy. *Antiviral Res.*, **27**, 419–424

Motimaya, A.M., Subramanya, K.S., Curry, P.T. & Kitchin, R.M. (1994) Evaluation of the genotoxic potential of selected anti-AIDS treatment drugs at clinical doses in vivo in mice. *Toxicol. Lett.*, **70**, 171–183

Nassar, M.N., Chen, T., Reff, M.J. & Agharkar, S.N. (1993) Didanosine. In: Brittain, H.G., ed., *Analytical Profiles of Drug Substances and Excipients*, New York, Academic Press, Vol. 22, pp. 185–227

National Cancer Institute (1992) *NCI Investigational Drugs—Chemical Information—1992* (NIH Publication No. 92-2654), Bethesda, MD, National Institutes of Health, pp. 83–85

Nordback, I.H., Olson, J.L., Chaisson, R.E. & Cameron, J.L. (1992) Acute effects of a nucleoside analog dideoxyinosine (DDI) on the pancreas. *J. surg. Res.*, **53**, 610–614

Perry, C.M. & Balfour, J.A. (1996) Didanosine. An update on its antiviral activity, pharmacokinetic properties and therapeutic efficacy in the management of HIV disease. *Drugs*, **52**, 928–962

Peter, K. & Gambertoglio, J.G. (1998) Intracellular phosphorylation of zidovudine (ZDV) and other nucleoside reverse transcriptase inhibitors (RTI) used for human immunodeficiency virus (HIV) infection. *Pharm. Res.*, **15**, 819–825

Phillips, K.E. & Munson, A.E. (1997) 2′,3′-Dideoxyinosine inhibits the humoral immune response in female B6C3F1 mice by targeting the B lymphocyte. *Toxicol. appl. Pharmacol.*, **145**, 260–267

Phillips, M.D., Nascimbeni, B., Tice, R.R. & Shelby, M.D. (1991) Induction of micronuclei in mouse bone marrow cells: An evaluation of nucleoside analogues used in the treatment of AIDS. *Environ. mol. Mutag.*, **18**, 168–183

Phillips, K.E., McCay, J.A., Brown, R.D., Musgrove, D.L., Meade, B.J., Butterworth, L.F., Wilson, S., White, K.L., Jr & Munson, A.E. (1997) Immunotoxicity of 2′,3′-dideoxyinosine in female B6C3F1 mice. *Drug chem. Toxicol.*, **20**, 189–228

Pike, I.M. & Nicaise, C. (1993) The didanosine Expanded Access Program: Safety analysis. *Clin. infect. Dis.*, **16** (Suppl. 1), S63–S68

Pluda, J.M., Venzon, D.J., Tosato, G., Lietzau, J., Wyvill, K., Nelson, D.L., Jaffe, E.S., Karp, J.E., Broder, S. & Yarchoan, R. (1993) Parameters affecting the development of non-Hodgkin lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. *J. clin. Oncol.*, **11**, 1099–1107

Pons, J.C., Boubon, M.C., Tgaburet, A.M., Singlas, E., Chambrin, V., Frydman, R., Papiernik, E. & Delfraissy, J.F. (1991) Fetoplacental passage of 2′,3′-dideoxyinosine (Letter to the Editor). *Lancet*, **337**, 732

Qian, M., Finco, T.S., Swagler, A.R. & Gallo, J.M. (1991) Pharmacokinetics of 2′,3′-dideoxyinosine in monkeys. *Antimicrob. Agents Chemother.*, **35**, 1247–1249

Raffi, F., Reliquet, V., Auger, S., Besnier, J.-M., Chennebault, J.-M., Billaud, E., Michelet, C., Perre, P., Lafeuillade, A., May, T. & Billaudel, S. (1998) Efficacy and safety of stavudine and didanosine combination therapy in antiretroviral-experienced patients. *AIDS*, **12**, 1999–2005

Ravasco, R.J., Unadkat, J.D., Tsai, C.-C. & Nosbisch, C. (1992) Pharmacokinetics of dideoxyinosine in pigtailed macaques (*Macaca nemestrina)* after intravenous and subcutaneous administration. *J. acquir. Immune Defic. Syndr.*, **5**, 1016–1018

Rote Liste Sekretariat (1998) *Rote Liste 1998*, Frankfurt, Rote Liste Service GmbH, pp. 10–450

Rozencweig, M., McLaren, C., Beltangady, M., Ritter, J., Canetta, R., Schacter, L., Kelley, S., Nicaise, C., Smaldone, L., Dunkle, L., Barbhaiya, R., Knupp, C., Cross, A., Tsianco, M. & Martin, R.R. (1990) Overview of phase I trials of 2′,3′-dideoxyinosine (ddI) conducted on adult patients. *Rev. infect. Dis.*, **12**, S570–S575

Sahai, J., Gallicano, K., Garber, G., Pakuts, A. & Cameron, W. (1995) Pharmacokinetics of simultaneously administered zidovudine and didanosine in HIV-seropositive male patients. *J. acquir. Immune Defic. Syndr.*, **10**, 54–60

Sandberg, J.A., Binienda, Z., Lipe, G., Rose, L.M., Parker, W.B., Ali, S.F. & Slikker, W., Jr (1995) Placental transfer and fetal disposition of 2′,3′-dideoxycytidine and 2′,3′-dideoxyinosine in the rhesus monkey. *Drug Metab. Dispos.*, **23**, 881–884

Schmued, L.C., Albertson, C.M., Andrews, A., Sandberg, J.A., Nickols, J. & Slikker, W., Jr (1996) Evaluation of brain and nerve pathology in rats chronically dosed with ddI or isoniazid. *Neurotoxicol. Teratol.*, **18**, 555–563

Seidlin, M., Lambert, J.S., Dolin, R. & Valentine, F.T. (1992) Pancreatitis and pancreatic dysfunction in patients taking dideoxyinosine. *AIDS*, **6**, 831–835

Sieh, E., Coluzzi, M.L., Cusella de Angelis, M.G., Mezzogiorno, A., Foridia, M., Canipari, R., Cossu, G. & Vella, S. (1992) The effects of AZT and DDI on pre- and postimplantation mammalian embryos: An in vivo and in vitro study. *AIDS Res. hum. Retroviruses*, **8**, 639–649

Simpson, D.M. & Tagliati, M. (1995) Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J. acquir. Immune Defic. Syndr. hum. Retrovirol.*, **9**, 153–161

Singlas, E., Taburet, A.M., Lebas, F.B., de Curzon, O.P., Sobel, A., Chauveau, P., Viron, B., Al Khayat, R., Poignet, J.L., Mignon, F., Humbert, G. & Fillastre, J.P. (1992) Didanosine pharmacokinetics in patients with normal and impaired renal function: Influence of hemodialysis. *Antimicrob. Agents Chemother.*, **36**, 1519–1524

Spruance, S.L., Pavia, A.T., Peterson, D., Berry, A., Pollard, R., Patterson, T.F., Frank, I., Remick, S.C., Thompson, M., MacArthur, R.D., Morey, G.E., Jr, Ramirez-Ronda, C.H., Bernstein, B.M., Sweet, D.E., Crane, L., Peterson, E.A., Pachucki, C.T., Green, S.L., Brand, J., Rios, A., Dunkle, L.M., Cross, A., Brown, M.J., Ingraham, P., Gugliotti, R., Schindzielorz, A.H. & Smaldone, L. for the Bristol-Myers Squibb AI454-010 Study Group (1994) Didanosine compared with continuation of zidovudine in HIV-infected patients with signs of clinical deterioration while receiving zidovudine. A randomized double-blind clinical trial. *Ann. intern. Med.*, **120**, 360–368

Swiss Pharmaceutical Society, ed. (1999) *Index Nominum, International Drug Directory*, 16th Ed., Stuttgart, Medpharm Scientific Publishers [MicroMedex CD-ROM]

Thomas, J., ed. (1998) *Australian Prescription Products Guide*, 27th Ed., Victoria, Australian Pharmaceutical Publishing, Vol. 1, pp. 2907–2912

US Pharmacopeial Convention (1998) *USP Dispensing Information*, Vol. I, *Drug Information for the Health Care Professional*, 18th Ed., Rockville, MD, pp. 1178–1182

Warner, W.A., Bregman, C.L., Comereski, C.R., Arezzo, J.C., Davidson, T.J., Knupp, C.A., Kaul, S., Durham, S.K., Wasserman, A.J. & Frantz, J.D. (1995) Didanosine (ddI) and stavudine (d4T): Absence of peripheral neurotoxicity in rabbits. *Food chem. Toxicol*., **33**, 1047–1050

Wientjes, M.G. & Au, J.L.-S. (1992a) Pharmacokinetics of oral 2′,3′-dideoxyinosine in rats. *Pharm. Res*., **9**, 822–825

Wientjes, M.G. & Au, J.L.-S. (1992b) Lack of pharmacokinetic interaction between intravenous 2′,3′-dideoxyinosine and 3′-azido-3′-deoxythymidine in rats. *Antimicrob. Agents Chemother*., **36**, 665–668

Wientjes, M.G., Placke, M.E., Chang, M.J.-W., Page, J.G., Kluwe, W.M. & Tomaszewski, J.E. (1991) Pharmacokinetics of 2′,3′-dideoxyadenosine in dogs. *Invest. new Drugs*, **9**, 159–168

Yarchoan, R., Pluda, J.M., Perno, C.F., Mitsuya, H., Thomas, R.V., Wyvill, K.M. & Broder, S. (1990a) Initial clinical experience with dideoxynucleosides as single agents and in combination therapy. *Ann. N.Y. Acad. Sci*., **616**, 328–343

Yarchoan, R., Mitsuya, H., Pluda, J.M., Marczyk, K.S, Thomas, R.V., Hartman, N.R., Brouwers, P., Perno, C.-F., Allain, J.-P., Johns, D.G. & Broder, S. (1990b) The National Cancer Institute phase I study of 2′,3′-dideoxyinosine administration in adults with AIDS or AIDS-related complex: Analysis of activity and toxicity profiles. *Rev. infect. Dis*., **12**, S522–S533

Youssef, J.A. & Badr, M.Z. (1992) Disruption of mitochondrial energetics and DNA synthesis by the anti-AIDS drug dideoxyinosine. *Toxicol. Lett*., **60**, 197–202