Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Videx EC 400 mg gastro-resistant hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant hard capsule contains 400 mg of didanosine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard

Gastro-resistant capsules are opaque white and embossed in red with "6674" on one half, and "BMS 400 mg" on the other half.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Videx is indicated in combination with other antiretroviral drugs for the treatment of HIV-1 infected patients only when other antiretrovirals cannot be used.

4.2 Posology and method of administration

Because didanosine absorption is reduced in the presence of food, Videx gastro−resistant capsules must be administered on an empty stomach (at least 2 hours before or 2 hours after a meal) (see section 5.2).

Posology

Videx gastro-resistant capsules are administered on a once daily or a twice daily regimen (see section 5.1).

The recommended total daily dose is based on patient body weight (kg):

- for patients weighing at least 60 kg: 400 mg per day
- for patients weighing less than 60 kg: 250 mg per day

The following table defines the administration schedule for all strengths of the gastro-resistant capsules:

Patient Weight	Total Daily Dose	Corresponding Regimen
at least 60 kg	400 mg	1 capsule of 400 mg (once daily) or 1 capsule of 200 mg (twice daily)
less than 60 kg	250 mg	1 capsule of 250 mg (once daily) or 1 capsule of 125 mg (twice daily)

Special populations

Elderly population: Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see below).

Renal impairment: The following dose adjustments are recommended:

Creatinine Clearance (ml/min) / Patient Weight	Total Daily Dose	
	at least 60 kg (dose, mg)	less than 60 kg (dose, mg)
at least 60	400 mg	250 mg
30 – 59	200 mg	150 mg*
10 – 29	150 mg*	100 mg*
less than 10	100 mg*	75 mg*

* These strengths of Videx gastro-resistant capsules are not available. An alternative Videx formulation is to be used.

The dose should preferably be administered after dialysis (see section 4.4). However, it is not necessary to administer a supplemental dose of Videx following haemodialysis.

Paediatric patients: Since urinary excretion is also a major route of elimination of didanosine in paediatric patients, the clearance of didanosine may be altered in paediatric patients with renal impairment. Although there are insufficient data to recommend a specific dosage adjustment of Videx in this patient population, a reduction in the dose and/or an increase in the interval between doses must be considered.

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population

Paediatric patients older than 6 years: The use of Videx gastro-resistant capsules has not been specifically studied in paediatric patients. The recommended daily dose (based on body surface area) is 240 mg/m^2.

Paediatric patients younger than 6 years: The gastro-resistant capsules should not be opened as there is a potential for inadvertent aspiration. Therefore, this medicine is contraindicated in this age group. Other more appropriate Videx formulations are available.

Method of administration

To optimise absorption, the gastro-resistant capsule should be taken intact with at least 100 ml of water. Patients should be instructed not to open the capsule to facilitate administration, since this could reduce absorption (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Paediatric patients younger than 6 years (risk of inadvertent aspiration).

Co-administration with stavudine due to the potential for serious and/or life-threatening events notably lactic-acidosis, liver function abnormalities, pancreatitis, and peripheral neuropathy (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Pancreatitis is a known serious complication among HIV infected patients. It has also been associated with didanosine therapy and has been fatal in some cases. Didanosine should be used only with extreme caution in patients with a history of pancreatitis. Positive relationships have been found between the risk of pancreatitis and daily dose of didanosine.

Whenever warranted by clinical conditions, didanosine should be suspended until the diagnosis of pancreatitis is excluded by appropriate laboratory and imaging techniques. Similarly, when treatment with other medicinal products known to cause pancreatic toxicity is required (e.g. pentamidine), didanosine should be suspended whenever possible. If concomitant therapy is unavoidable, there should be close observation. Dose interruption should be considered when biochemical markers of pancreatitis have significantly increased, even in the absence of symptoms. Significant elevations of triglycerides are a known cause of pancreatitis and warrant close observation.

Lactic acidosis: lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of didanosine. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.
Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with didanosine should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels. Caution should be exercised when administering didanosine to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely. (See also section 4.6).

Liver disease: Liver failure of unknown aetiology has occurred rarely in patients on didanosine. Patients should be observed for liver enzyme elevations and didanosine should be suspended if enzymes rise to more than 5 times the upper limit of normal. Rechallenge should be considered only if the potential benefits clearly outweigh the potential risks.

The safety and efficacy of didanosine has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Non-cirrhotic Portal Hypertension: Postmarketing cases of non-cirrhotic portal hypertension have been reported, including cases leading to liver transplantation or death. Cases of didanosine-associated non-cirrhotic portal hypertension were confirmed by liver biopsy in patients with no evidence of viral hepatitis. Onset of signs and symptoms ranged from months to years after start of didanosine therapy. Common presenting features included elevated liver enzymes, esophageal varices, hematemesis, ascites, and splenomegaly.

Patients receiving didanosine should be monitored for early signs of portal hypertension (eg, thrombocytopenia and splenomegaly) during routine medical visits. Appropriate laboratory testing including liver enzymes, serum bilirubin, albumin, complete blood count, and international normalized ratio (INR) and ultrasonography should be considered. Didanosine should be discontinued in patients with evidence of non-cirrhotic portal hypertension.

Peripheral neuropathy: Patients on didanosine may develop toxic peripheral neuropathy, usually characterised by bilateral symmetrical distal numbness, tingling, and pain in feet and, less frequently, hands. If symptoms of peripheral neuropathy develop, patients should be switched to an alternative treatment regimen.

Retinal or optic nerve changes: Patients on didanosine have rarely experienced retinal or optic nerve lesions, particularly at doses above those currently recommended. An ophthalmologic examination including visual acuity, color vision, and a dilated fundus examination is to be considered on a yearly basis as well as in case of occurrence of visual changes, in patients treated with didanosine.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jiroveci (formerly known as Pneumocystis carinii) pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Lipoatrophy: on the basis of mitochondrial toxicity, didanosine has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs, and buttocks.

Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis: although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections: Patients receiving didanosine or any antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection or therapy. They therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Interaction with other medicinal products:
Tenofovir: Co-administration of didanosine and tenofovir disoproxil fumarate results in a 40−60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse events (see section 4.5). Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported.
A reduced didanosine dose (250 mg) has been tested to avoid over-exposure to didanosine in case of co-administration with tenofovir disoproxil fumarate, but this has been associated with reports of high rate of virological failure and of emergence of resistance at early stage within several tested combinations.
Co-administration of didanosine and tenofovir disoproxil fumarate is therefore not recommended, especially in patients with high viral load and low CD4 cell count. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. If this combination is judged strictly necessary, patients should be carefully monitored for efficacy and didanosine related adverse events.

Ganciclovir and valganciclovir: Co-administration of didanosine with ganciclovir or valganciclovir may result in didanosine-associated toxicities. Patients should be closely monitored (see section 4.5).

Not recommended combinations:
Pancreatitis (fatal and nonfatal) and peripheral neuropathy (severe in some cases) have been reported in HIV infected patients receiving didanosine in association with hydroxyurea and stavudine (see section 4.3 and 4.5). Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV infected patients treated with antiretroviral agents and hydroxyurea; fatal hepatic events were reported most often in patients treated with

stavudine, hydroxyurea and didanosine. Hence, this combination must be avoided.

Allopurinol: Co-administration of didanosine and allopurinol results in increased systemic exposure to didanosine, which can result in didanosine-associated toxicity. Therefore, co-administration of allopurinol and didanosine is not recommended. Patients treated with didanosine who require allopurinol administration should be switched to an alternative treatment regimen (see section 4.5).

Co-administration of ribavirin and didanosine is not recommended due to an increased risk of adverse events, in particular of mitochondrial toxicity (see section 4.5).

Triple nucleoside therapy: There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when didanosine was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen.

Patients on sodium restricted diet:
125 mg: Each gastro-resistant capsule contains 0.53 mg sodium.
200 mg: Each gastro-resistant capsule contains 0.85 mg sodium.
250 mg: Each gastro-resistant capsule contains 1.0 mg sodium.
400 mg: Each gastro-resistant capsule contains 1.7 mg sodium.

Paediatric population

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any paediatric patient exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative paediatric patients, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of didanosine with medicines that are known to cause peripheral neuropathy or pancreatitis may increase the risk of these toxicities. Patients who receive these medicines should be carefully observed.

Not recommended for concomitant use
Ribavirin: Based on *in vitro* data, ribavirin increases the intracellular triphosphate levels of didanosine. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving didanosine and ribavirin with or without stavudine. Co-administration of ribavirin and didanosine is not recommended (see section 4.4).

Tenofovir: The co-administration of didanosine and tenofovir disoproxil fumarate is not recommended (see Table 1 and section 4.4).

Allopurinol: Co-administration of allopurinol (a xanthine oxidase inhibitor) with didanosine is not recommended. Patients treated with didanosine who require allopurinol administration should be switched to an alternative treatment regimen (see Table 1 and section 4.4). Xanthine oxidase is an enzyme involved in the metabolism of didanosine. Other inhibitors of xanthine oxidase may increase exposure to didanosine when administered concomitantly and thus increase the potential for didanosine associated undesirable effects. Patients should be closely monitored for didanosine related undesirable effects (see section 4.8).

Other interactions
Interactions between didanosine and antiretroviral agents or other non−antiretroviral medicinal products are listed in

Table 1 below (increase is indicated as "↑", decrease is indicated as "↓", no change as "↔"). Unless otherwise noted, studies were conducted in HIV-infected patients.

Table 1: Interactions between didanosine and other medicinal products

Medicinal product by therapeutic areas (dose in mg)	Effects on drug levels Mean percent change in AUC, C_{max}	Recommendation concerning co−administration with didanosine
ANTI-INFECTIVES		
Antiretrovirals		
Non-Nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs)		
Etravirine/Didanosine buffered tablet (200 mg twice daily / 400 mg single dose)	Didanosine: AUC: ↔ C_{max}: ↔ Etravirine: AUC: ↔ C_{max}: ↔	No dose adjustment is necessary for either medicinal product.
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Stavudine / Didanosine buffered tablet (40 mg every 12 hours for 4 days / 100 mg every 12 hours for 4 days)	Didanosine: AUC: ↔ C_{max}: ↔ Stavudine: AUC: ↔ C_{max}: ↑ 17%	This combination is contraindicated given that both drugs exhibits high risk of mitochondrial toxicity (see section 4.3 and 4.4).
Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure	Co-administration of didanosine and tenofovir disoproxil fumarate is not recommended.

	within several tested combinations for the treatment of HIV-1 infection.	
Zidovudine / Didanosine (200 mg every 8 hours for 3 days / 200 mg every 12 hours for 3 days)	Didanosine: AUC: ↔ C_{max}: ↔ Zidovudine: AUC: ↓ 10% C_{max}: ↓ 16.5%	No dose adjustment is necessary for either medicinal product.
Protease Inhibitors		
Darunavir/ Ritonavir/Didanosine gastro-resistant capsules (600 mg administered with low−dose ritonavir twice daily / 400 mg once daily)	Didanosine (administered on an empty stomach 2 hours prior to darunavir/ritonavir given with food.): AUC: ↓ 9% C_{max}: ↓ 16% Darunavir (co-administered with low dose ritonavir): AUC: ↔ C_{max}: ↔	No dose adjustment is necessary for either medicinal product.
Indinavir / Didanosine gastro-resistant capsules (800 mg single dose / 400 mg single dose)	Indinavir: AUC: ↔ C_{max}: ↔	No dose adjustment is necessary for either medicinal product.
Antibiotics		
Ciprofloxacin / Didanosine gastro-resistant capsules (750 mg single dose / 400 mg single dose)	Ciprofloxacin: AUC: ↔ C_{max}: ↔	No dose adjustment is necessary for either medicinal product.
Dapsone / Didanosine buffered tablet (100 mg single dose / 200 mg every 12 hours for 14 days)	Dapsone: AUC: ↔ C_{max}: ↔	No dose adjustment is necessary for either medicinal product.
Ganciclovir / Didanosine buffered tablet (1000 mg every 8 hours / 200 mg every 12 hours) Valganciclovir	Didanosine (ganciclovir administered concurrent with or 2 hours after): $AUC_{steady-state}$: ↑ 111% C_{max}: not available Ganciclovir (administered 2 hours after but not concurrent with didanosine): $AUC_{steady-state}$: ↓ 21% C_{max}: not available Although the magnitude of	Patients taking didanosine in combination with ganciclovir and valganciclovir should be closely monitored for didanosine-associated toxicities.

	increase in didanosine exposure when co-administered with valganciclovir has not been established, an increase in didanosine exposure would be anticipated when these agents are co-administered.	
Rifabutin / Didanosine buffered tablet (300 or 600 mg per day for 12 days / 167 or 250 mg every 12 hours for 12 days)	Didanosine: AUC: ↑ 13% C_{max}: ↑ 17%	No dose adjustment is necessary for either medicinal product.
Sulfamethoxazole / Didanosine buffered tablet (1000 mg single dose / 200 mg single dose)	Didanosine: AUC: ↔ C_{max}: ↔ Sulfamethoxazole: AUC: ↓ 11% C_{max}: ↓ 12%	No dose adjustment is necessary for either medicinal product.
Trimethoprim / Didanosine buffered tablet (200 mg single dose / 200 mg single dose)	Didanosine: AUC: ↔ C_{max}: ↑ 17% Trimethoprim: AUC: ↑ 10% C_{max}: ↓ 22%	No dose adjustment is necessary for either medicinal product.
ACID REDUCING AGENTS		
H2-Receptor antagonists		
Ranitidine / Didanosine buffered tablet (150 mg single dose, 2 hours before didanosine / 375 mg single dose)	Didanosine: AUC: ↑ 14% C_{max}: ↑ 13% Ranitidine: AUC: ↓ 16% C_{max}: ↔	No dose adjustment is necessary for either medicinal product.
ANTI-EMESIS AGENTS		
Metoclopramide / Didanosine buffered tablet (10 mg single dose / 300 mg single dose)	Didanosine: AUC: ↔ C_{max}: ↑ 13%	No dose adjustment is necessary for either medicinal product.
ANTI-GOUT AGENTS		
Allopurinol / Didanosine buffered tablet (healthy volunteer, 300 mg once daily for 7 days / 400 mg single dose at Day 1 and Day 8)	Didanosine: AUC: ↑ 105% C_{max}: ↑ 71%	Co-administration of didanosine and allopurinol is not recommended. Patients treated with didanosine who require allopurinol administration should be switched to an alternative treatment regimen and be

		closely monitored for didanosine related undesirable effects.
OPIOIDS		
Loperamide / Didanosine buffered tablet (4 mg every 6 hours for 1 day / 300 mg single dose)	Didanosine: AUC: ↔ C_{max}: ↓ 23%	No dose adjustment is necessary for either medicinal product.
Methadone / Didanosine buffered tablet (chronic maintenance dose / 200 mg single dose) gastro-resistant capsules (chronic maintenance dose / 400 mg single dose)	Didanosine: AUC: ↓ 57% C_{max}: ↓ 66% AUC: ↓ 29% C_{max}: ↓ 41%	If didanosine is used in combination with methadone, patients should be closely monitored for adequate clinical response.

Unlike the Videx chewable/dispersible tablets, Videx gastro-resistant capsules do not contain antacids and therefore drug interactions mediated by altered gastric pH are not anticipated when Videx gastro-resistant capsules are co-administered with medicinal products where absorption is influenced by gastric acidity. Specific interaction studies with ciprofloxacin, indinavir, ketoconazole, itraconazole and fluconazole showed no evidence of clinically significant interaction (Table 1).

Ingestion of Videx with food alters the pharmacokinetics of didanosine (see section 5.2).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of didanosine in pregnant women and it is not known whether didanosine can cause foetal harm or affect reproductive capacity when administered during pregnancy. Lactic acidosis (see section 4.4), sometimes fatal, has been reported in pregnant women who received the combination of didanosine and stavudine with or without other antiretroviral treatment. Therefore, the use of didanosine during pregnancy should be considered only if clearly indicated, and only when the potential benefit outweighs the possible risk.

Teratology studies in rats and rabbits did not produce evidence of embryotoxic, foetotoxic, or teratogenic effects. A study in rats showed that didanosine and/or its metabolites are transferred to the foetus through the placenta.

Breastfeeding

It is unknown whether didanosine is excreted in human milk. It is recommended that women taking didanosine do not breast-feed because of the potential for serious adverse reactions in nursing infants.

At the 1000 mg/kg/day dose levels in rats, didanosine was slightly toxic to females and pups during mid and late lactation (reduced food intake and body weight gains), but the physical and functional development of the subsequent offspring were not impaired. A further study showed that, following oral administration, didanosine and/or its metabolites were excreted in the milk of lactating rats.

Fertility

In rats, didanosine did not impair the reproduction ability of male or female parents following treatment prior to and during mating, gestation and lactation at daily didanosine doses up to 1000 mg/kg/day. In a perinatal and postnatal reproduction study in rats, didanosine did not induce toxic effects.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Most of the serious adverse events observed have generally reflected the recognised clinical course of HIV infection.

In data collected earlier involving monotherapy regimens, no different safety concerns were seen compared to the triple regimen data presented below. In comparative studies between Videx once daily and twice daily (tablets), no significant difference in terms of incidence of pancreatitis and peripheral neuropathy has been shown.

Pancreatitis, which may be fatal in some cases, was reported in <1% of the patients receiving Videx gastro-resistant capsule; patients with advanced HIV disease or a history of pancreatitis may be at increased risk of developing pancreatitis (see sections 4.2 and 4.4).

Peripheral neurologic symptoms (8%) have been associated with Videx (see section 4.4).

Adverse reactions of moderate or greater severity with at least a possible relationship to treatment regimen (based on investigators' attribution) reported from an open label clinical study (study−148), involving 482 patients treated with Videx tablet plus stavudine and nelfinavir, and in a clinical study (study−152) evaluating Videx gastro-resistant capsules as part of a triple regimen in 255 treatment naive HIV infected adults are listed. Also listed are adverse reactions observed post-approval in association with Videx-containing antiretroviral treatment regimens.
The frequency of adverse reactions listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations:	uncommon: sialoadenitis*
Blood and lymphatic system disorders:	uncommon: anemia*, leukopenia*, thrombocytopenia*
Immune system disorders:	uncommon: anaphylactic reaction**
Metabolism and nutrition disorders:	common: anorexia* uncommon: lactic acidosis*, diabetes mellitus*, hypoglycaemia**, hyperglycaemia*
Nervous system disorders:	common: peripheral neurologic symptoms (including neuropathy), headache
Eye disorders:	uncommon: dry eyes*, retinal depigmentation**, optic neuritis**
Gastrointestinal disorders:	very common: diarrhoea common: nausea, vomiting, abdominal pain, flatulence*, dry mouth* rare: parotid gland enlargement*
Hepatobiliary disorders:	common: hepatitis* uncommon: hepatic steatosis*, liver failure** rare: non-cirrhotic portal hypertension* (see

	section 4.4)
Skin and subcutaneous tissue disorders:	common: rash uncommon: alopecia*
Musculoskeletal and connective tissue disorders	common: myalgia (with or without increases in creatine phosphokinase)*, arthralgia* uncommon: rhabdomyolysis including acute renal failure and haemodialysis** rare: myopathy*
Reproductive system and breast disorders:	common: gynaecomastia*
General disorders and administration site conditions:	common: fatigue, asthenia*, chills and fever*, pain*
Investigations:	common: increased/abnormal serum amylase*, increased/abnormal creatine phosphokinase* uncommon: increased/abnormal alkaline phosphatase*

* Adverse reactions observed in post-marketing clinical trials in association with didanosine-containing antiretroviral treatment

** This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to Videx in randomised controlled clinical trials and compassionate use (n=1873)

Laboratory abnormalities:

Laboratory abnormalities (grade 3-4) reported in studies −148 (tablets) and −152 (gastro-resistant capsules) included increase of lipase in 7% and 5% respectively, increase of ALT in 3% and 6% respectively, increase of AST in 3% and 5%, respectively, increase in uric acid in 2% in both studies, and increase of bilirubin in 1% and < 1% respectively, of the patients. Neutropenia (grade 3-4) was reported in 2% in both studies −148 and −152, anemia in < 1% and 1% in study −148 and in study −152 respectively, and thrombocytopenia in 1% and < 1%, respectively, of the patients.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Lipoatrophy

Didanosine has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs and buttocks. The incidence and severity of lipoatrophy are related to cumulative exposure, and is often not reversible when didanosine treatment is stopped. Patients receiving Videx should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Videx should not be continued (see section 4.4).

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Osteonecrosis: cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis have been

reported with the use of didanosine (see section 4.4).

Paediatric population

Safety data for paediatric patients were generally similar to those seen in adults. A higher haematotoxicity has been reported with the combination with zidovudine compared to didanosine monotherapy. Retinal or optic nerve changes have been reported in a small number of paediatric patients usually at doses above those recommended (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no known antidote for didanosine overdosage. Experience in early studies, in which didanosine was initially administered at doses ten times the recommended doses, indicates that the anticipated complications of overdosage could include pancreatitis, peripheral neuropathy, hyperuricemia and hepatic dysfunction.

Didanosine is not dialysable by peritoneal dialysis, although there is some clearance by haemodialysis. (The fractional removal of didanosine during an average haemodialysis session of 3 to 4 hours was approximately 20−35% of the dose present in the body at the start of dialysis.)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitor, ATC Code: J05AF02

Mechanism of action
After didanosine (2', 3'-dideoxyinosine) enters the cell, it is enzymatically converted to dideoxyadenosine-triphosphate (ddATP), its active metabolite. In viral nucleic acid replication, incorporation of this 2', 3'-dideoxynucleoside prevents chain extension, and thereby inhibits viral replication.

In addition, ddATP inhibits HIV-reverse transcriptase by competing with dATP for binding to the enzyme's active site, preventing proviral DNA synthesis.

Antiviral activity *in vitro*
Didanosine is an inhibitor of HIV-1 and HIV-2 replication in cultured human cells and cell lines.

Resistance
Current evidence indicates that the incidence of resistance to didanosine is an infrequent event and the resistance generated is modest in degree. Didanosine-resistant isolates have been selected *in vivo* and are associated with specific genotype changes in the reverse transcriptase codon region (codons L74V (most prevalent), K65R, M184V and T69S/G/D/N). Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. Mutant viruses containing the L74V substitution show a decline in viral fitness and these mutants quickly revert to wild type in the absence of didanosine.

Cross-resistance
Cross-resistance between didanosine and any antiretroviral class except nucleoside reverse transcriptase inhibitor (NRTIs) is unlikely. Cross-resistance between didanosine and NRTIs is observed in isolates containing multi-resistant mutations such as the Q151M complex, K65R, 3 or more thymidine analog mutations (TAMs), T69ins or multiple nucleoside analogue associated mutations (NAMs).

Clinical results

Using the Videx tablet formulation, the effect of Videx twice daily administration, alone or in combination with zidovudine, was evaluated in several major randomised, controlled clinical trials (ACTG 175, ACTG 152, DELTA, CPCRA 007). These trials confirmed the reduced risk of HIV disease progression or death with Videx tablets therapy, alone or in combination with zidovudine, as compared with zidovudine monotherapy in HIV infected individuals, including symptomatic and asymptomatic adults with CD4 counts < 500 cells/mm^3 and paediatric patients with evidence of immunosuppression. The primary demonstration of clinical benefits of didanosine has been made through the ACTG 175 trial with the buffered tablet formulation of Videx administered twice daily. This study showed that 8 weeks of treatment with zidovudine (200 mg) three times daily, Videx tablets (200 mg) twice daily, or Videx tablets (200 mg) twice daily plus zidovudine (200 mg) three times daily decreased mean plasma HIV RNA by 0.26, 0.65 and 0.93 log_{10} copies/ml, respectively.

In antiretroviral naive patients
The efficacy of Videx tablet or powder was evaluated in treatment-naive HIV infected patients in two (48-week) randomised open label clinical trials.

Study START II (n=205) was a multicenter, randomized, open label study comparing Videx (200 mg or 125 mg if weight <60 kg) twice daily plus stavudine (40 mg or 30 mg if weight <60 kg) twice daily and indinavir (800 mg) three times daily to zidovudine (200 mg) three times daily plus lamivudine (150 mg) twice daily and indinavir (800 mg) three times daily. Through 48 weeks of treatment, results were in favour of the Videx arm. However, no formal conclusion can be drawn on the equivalence of the two regimens.

Since didanosine exhibits a very long intracellular half-life (> 24 hours), permitting the accumulation of its pharmacologically active ddATP-moiety for extended time periods, administration of the total daily dose of Videx in a once daily dosing regimen has been explored through clinical studies.

Study –148 (n= 756) was a randomised open label study comparing Videx (400 mg or 250 mg if weight < 60 kg) once daily plus stavudine (40 mg or 30 mg if weight <60 kg) twice daily and nelfinavir (750 mg) three times daily to zidovudine (300 mg) twice daily plus lamivudine (150 mg) twice daily and nelfinavir (750 mg) three times daily (Table 2). After 48 weeks of treatment, results were in favour of the zidovudine, lamivudine and nelfinavir arm compared to Videx, stavudine and nelfinavir arm in terms of proportion of patients with undetectable viral load (the proportion of patients with HIV RNA copies < 400 copies/ml was 53% for the Videx-containing arm and 62% for the comparator). However, no formal conclusions can be drawn on this study due to methodological issues.

Table 2: Outcome of Randomized Treatment at Week 48 (Study -148)

Parameter	**Videx + stavudine + nelfinavir n=503**	**zidovudine + lamivudine + nelfinavir n=253**
HIV RNA < 400 copies/ml, treatment response, %		
-	53	62
HIV RNA < 50 copies/ml, treatment response, %		
-	37	47
HIV RNA Mean Change from Baseline, log_{10} copies/ml		
-	-2.46 (n=321**a**)	-2.65 (n=173**a**)
CD4 Mean Change from Baseline, cells/mm^3		
-	208.5 (n=320**a**)	215.7 (n=173**a**)

a Number of patients evaluable.

The efficacy of Videx gastro-resistant capsules was evaluated in treatment-naive HIV infected adults as part of a triple

regimen in two (48-week) randomised open label clinical trials.

Study –152 (n= 511) was a 48-week, randomized, open-label study comparing Videx gastro-resistant capsules (400 mg once daily) plus stavudine (40 mg twice daily) and nelfinavir (750 mg three times daily) to zidovudine plus lamivudine (300 mg + 150 mg in combination twice daily) and nelfinavir (750 mg three times daily) (Table 3). The protocol-defined analysis showed the proportion of patients with HIV RNA levels < 400 copies/ml at week 48 to be similar for the Videx gastro-resistant arm and for the comparator. Similar $\log_{10}$ plasma HIV RNA decreases from baseline (Time Averaged Difference) were observed between treatment arms.

In study -158 (n= 138) the antiviral activity and tolerability of Videx gastro-resistant capsules (400 mg or 250 mg if weight <60 kg) were compared to tablets (400 mg or 250 mg if weight <60 kg), each given once daily in combination with stavudine (40 mg twice daily) and nelfinavir (750 mg three times daily). At 48 weeks of follow-up, there were similar $\log_{10}$ plasma HIV RNA decreases from baseline (Time Averaged Difference) between treatment arms. The percentages of patients with undetectable viral load (limit of detection < 400 copies/ml) were of the same magnitude between the two Videx arms. Due to the high drop-out rate (> 50%) in this study, no definitive conclusion could be drawn on the long-term data. The efficacy of Videx gastro-resistant capsules has not been established in advanced disease or in highly antiretroviral experienced patients.

Table 3: Outcome of Randomized Treatment at Week 48 (Study -152)

Parameter	**Videx (capsule) + stavudine + nelfinavir n=258**	**Zidovudine + lamivudine + nelfinavir n=253**
HIV RNA < 400 copies/ml, treatment response, %		
	56	53
HIV RNA < 50 copies/ml, treatment response, %		
	37	35
HIV RNA Mean Change from Baseline, $\log_{10}$ copies/ml		
	-2.51 (n=194**a**)	-2.51 (n=185**a**)
CD4 Mean Change from Baseline, cells/mm^3		
	157.3 (n=188**a**)	188.6 (n=183**a**)

a Number of patients evaluable.

In treatment experienced patients
Study –147 (n= 123) was a randomized open label two-arm study comparing Videx (400 mg or 250 mg if weight <60 kg) once daily versus Videx (200 mg or 125 mg if weight <60 kg) twice daily, in combination with stavudine and zidovudine. In the tritherapy setting, the study indicates that, in mostly asymptomatic patients that were stable on their first combination therapy containing Videx twice daily, the shift to a similar combination therapy with Videx once daily did not impact at short term (24 weeks) on the existing antiviral efficacy.

5.2 Pharmacokinetic properties

Absorption: Didanosine is rapidly degraded at an acidic pH. Therefore, the granules in the Videx gastro-resistant capsules release didanosine into the higher pH of the small intestine.

Compared to the fasting condition, the administration of Videx gastro-resistant capsules with a high fat meal significantly decreases the didanosine AUC (19%) and C_{max}(46%). Co−administering Videx gastro-resistant capsules with a light meal, 1 hour before or 2 hours after a light meal, results in a significant decrease in both AUC (27%, 24% and 10% respectively) and C_{max} of didanosine (22%, 15% and 15% respectively) compared to the fasting condition.

In another study, administration of Videx gastro-resistant capsules 1.5, 2 and 3 hours prior to a light meal results in equivalent C_{max} and AUC values compared to those obtained under fasting conditions.
To minimise the impact of food on the didanosine pharmacokinetics, Videx gastro-resistant capsules should be administered on an empty stomach at least 2 hours before or 2 hours after a meal (see section 4.2).

Relative to administration of intact Videx gastro-resistant capsule on empty stomach, co-administration of didanosine enteric coated beadlets sprinkled on yoghurt and applesauce resulted in a significant decrease in the AUC (20% and 18%, respectively) and C_{max} (30% and 24%, respectively).

Equivalent values for AUC are observed for the tablet and capsule formulations of Videx in healthy volunteers and subjects infected with HIV. The rate of absorption from Videx capsules is slower compared to the tablet; the value for C_{max} for the gastro-resistant capsule is 60% of the value for the tablet. The time to reach C_{max} is approximately 2 hours for the Videx gastro-resistant capsule and 0.67 hour for the Videx tablet.

In 30 patients receiving didanosine 400 mg once daily in the fasted state as Videx gastro-resistant capsules, single dose AUC was 2432 ± 919 ng·h/ml (38%) (mean ± SD [%CV]) and C_{max} was 933 ± 434 ng/ml (47%).

Distribution: The volume of distribution at steady state averages 54 l, suggesting that there is some uptake of didanosine by body tissues. The level of didanosine in the cerebrospinal fluid (CSF), one hour after infusion, averages 21% of that of the simultaneous plasma level.

Biotransformation: The metabolism of didanosine in man has not been evaluated. However, based on animal studies, it is presumed that it follows the same pathways responsible for the elimination of endogenous purines.

Elimination: The average elimination half-life after IV administration of didanosine is approximately 1.4 hours. Renal clearance represents 50% of total body clearance (800 ml/min), indicating that active tubular secretion, in addition to glomerular filtration, is responsible for the renal elimination of didanosine. Urinary recovery of didanosine is approximately 20% of the dose after oral treatment. There is no evidence of didanosine accumulation after the administration of oral doses for 4 weeks.

Hepatic impairment: No significant changes in the pharmacokinetics of didanosine were observed among haemophiliac patients with chronic, persistent elevations in liver function enzymes (n= 5), which may be indicative of impaired hepatic function; haemophiliac patients with normal or less severe increases in liver function enzymes (n= 8); and non-haemophiliac patients with normal enzyme levels (n= 8) following a single IV or oral dose. The pharmacokinetics of didanosine has also been studied in 12 non-HIV infected patients with moderate (n=8) to severe (n=4) hepatic impairment (Child-Pugh Class B or C). Mean AUC and Cmax values following a single 400 mg didanosine dose were approximately 13% and 19% higher, respectively, in patients with hepatic impairment compared to matched healthy subjects. AUC and C_{max} values in these patients with hepatic impairment were similar to those observed in healthy subjects from other studies and are within the pharmacokinetic variability of didanosine (see section 4.2).

Renal impairment: The half-life of didanosine after oral administration increased from an average of 1.4 hours in subjects with normal renal function to 4.1 hours in subjects with severe renal impairment requiring dialysis. After an oral dose, didanosine was not detectable in peritoneal dialysis fluid; recovery in haemodialysate ranged from 0.6% to 7.4% of the dose over a 3−4 hour dialysis period. Patients with a creatinine clearance < 60 ml/min may be at greater risk of didanosine toxicity due to decreased drug clearance. A dose reduction is recommended for these patients (see section 4.2).

Paediatric population

There are no specific pharmacokinetic data from paediatric patients treated with Videx gastro-resistant capsules.

5.3 Preclinical safety data

The lowest dose to cause death in acute toxicity studies in the mouse, rat and dog was greater than 2000 mg/kg which is equivalent to approximately 300 times the maximum recommended human dose (tablet).

Repeated dose toxicity: Repeat-dose oral toxicity studies revealed evidence of a dose-limiting skeletal muscle toxicity in rodents (but not in dogs) following long-term (> 90 days) dosing with didanosine at doses that were approximately

1.2 − 12 times the estimated human dose. Additionally, in repeat dose studies, leukopenia was observed in dogs and rats, and gastrointestinal disturbances (soft stool, diarrhoea) were seen in dogs at doses approximately 5 − 14 times the maximum human dose.

Carcinogenicity: In the carcinogenicity studies, non-neoplastic alterations have been observed including skeletal muscle myopathy, hepatic alterations and an exacerbation of spontaneous age-related cardiomyopathy.
Lifetime dietary carcinogenicity studies were conducted in mice and rats for 22 or 24 months, respectively. No drug-related neoplasms were observed in any didanosine-treated groups of mice during, or at the end of, the dosing period. In rats, statistically significant increased incidences of granulosa cell tumours in females receiving the high dose, of subcutaneous fibrosarcomas and histiocytic sarcomas in males receiving the high dose and of haemangiomas in males receiving the high and intermediate dose of didanosine were noted. The drug-relationship and clinical relevance of these statistical findings were not clear.

Genotoxicity: Results from the genotoxicity studies suggest that didanosine is not mutagenic at biologically and pharmacologically relevant doses. At significantly elevated concentrations *in vitro*, the genotoxic effects of didanosine are similar in magnitude to those seen with natural DNA nucleosides.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Carmellose sodium
Diethyl phthalate
30% methacrylic acid copolymer dispersion (EUDRAGIT L30D-55)
Sodium starch glycolate (Type A)
Talc
Sodium hydroxide (for pH adjustment)

Capsule shell:
Gelatin
Sodium laurilsulfate
Titanium dioxide (E171)

Capsule shell imprints (edible ink):
Shellac
Propylene glycol
Ammonium hydroxide
Simethicone
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polyvinyl Chloride/Polyethylene/ACLAR/Aluminium foil blisters with 10 hard capsules per blister card and 3 cards (30 capsules) per carton or with 10 hard capsules per blister card and 6 cards (60 capsules) per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals uc,
Plaza 254, Blanchardstown Corporate Park 2, Ballycoolin,
Dublin 15, D15 T867,
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