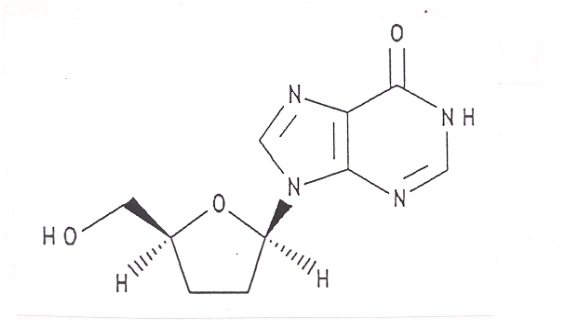
Data Sheet

Name of Medicine

Videx EC (didanosine)

DESCRIPTION

The chemical name for didanosine is 2',3'-dideoxyinosine. Didanosine is a white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and molecular weight of 236.2, and has the following structural formula:



Presentation

Videx **EC** (didanosine) Capsules are white, opaque, imprinted capsules, supplied in Bottles of 30 capsules.

Strength	***Capsule Imprint***	***Imprint colour***
125mg	BMS 125mg 6671	Tan
200mg	BMS 200mg 6672	Green
250mg	BMS 250mg 6673	Blue
400mg	BMS 400mg 6674	Red

Uses

Actions

Videx EC, a synthetic purine nucleoside analogue of deoxyadenosine, is an inhibitor of the *in vitro* replication of the Human Immunodeficiency Virus, HIV (also known as HTLV III, LAV or ARV) in human primary cell cultures and in established cell lines. The chemical name for **Videx EC** is 2',3' dideoxyinosine; it is also called ddI.

After **Videx EC** enters the cell, it is converted by cellular enzymes to the active antiviral metabolite, dideoxyadenosine triphosphate (ddATP). The intracellular half-life of ddATP, calculated from results obtained from *in vitro* cell culture studies, varied from 8 to 24 hours. A common feature of dideoxynucleosides [the class of compounds to which **Videx EC** (**didanosine**) belongs] is the lack of a free 3'-hydroxyl group. In nucleric acid replication, the 3'-hydroxyl of a naturally occurring nucleoside is the acceptor for covalent attachment of subsequent nucleoside 5'-monophosphates; its presence is therefore requisite for continued DNA chain extension. Because ddATP lacks a 3'-hydroxyl group, incorporation of ddATP into viral DNA leads to chain termination and, thus, inhibition of viral replication. In addition, ddATP further contributes to inhibition of viral replication through interference with the HIV-RNA dependent DNA polymerase (reverse transcriptase) by competing with the natural nucleoside triphosphate, dATP, for binding to the active side of the enzyme.
Didanosine has shown *in vitro* antiviral activity in a variety of HIV-infected T cell and monocyte/macrophage cell cultures. The concentration of medicine necessary to inhibit viral replication 50% (ID_{50}) has been reported to range from 2.5 to 10μM (1μM = 0.24 μg/mL) in T cells and from 0.01 to 0.1 μM in monocyte/macrophage cell cultures.

In a quantitative plaque (syncytium) reduction assay using HT4-6C cells, didanosine ID_{50} values of 2.1 μM for HIV-1 and 5.6 μM for HIV-2 have been reported. The ID_{50} values of zidovudine determined using this assay system were 0.05 and 0.08 μM for HIV-1 and HIV-2, respectively. However, in infected human MT-2 cells in culture, didanosine ID_{50} values reported for HIV-1 and HIV-2 were 1 and 10 μM, while ID_{50} values for zidovudine were 0.3 and > 100 μM respectively.

Pharmacokinetics

Absorption:
In healthy volunteers, as well as subjects infected with HIV, the area under the plasma concentration time curve (AUC) is equivalent for didanosine administered as the **Videx EC** capsule formulation relative to Videx buffered tablets. The peak plasma concentration (C_{MAX}) of didanosine, administered as **Videx EC** capsules, is reduced approximately 40% relative to Videx buffered tablets. The time to peak concentration (T_{MAX}) increases from approximately 0.67 hours for Videx buffered tablets to 2.0 hours for **Videx EC** capsules.

Effect of Food on Oral Absorption:

Videx EC should be administered on an empty stomach. A study in 8 asymptomatic HIV seropositive patients demonstrated that the administration of didanosine tablets within 5 minutes of a meal resulted in a 50% decrease in mean C_{max} and AUC values.

Distribution in Adults:

The steady state volume of distribution after IV administration averaged 54L. In a study of 5 adults, the concentration of didanosine in the cerebrospinal fluid one hour after infusion of didanosine averaged 21% of the simultaneous plasma concentration.

Metabolism:

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 in Adults:

After oral administration of didanosine, the average elimination half-life was 1.6 hours. Total body clearance averaged 800 mL/min. Renal clearance represented approximately 50% of the total body clearance, when didanosine was administered either intravenously or orally. This indicates that active tubular secretion, in addition to glomerular filtration, is responsible for the renal elimination of didanosine. Urinary recovery of didanosine after a single dose was approximately 55%, and 20% of the dose after IV and oral administration, respectively. There was no evidence of accumulation of didanosine after either IV or oral dosing.

The pharmacokinetics of didanosine have not been studied in patients over 65 years of age (**see Precautions- Elderly patients**)

Indications

Videx EC in combination with other antiretroviral drugs, is indicated for the treatment of HIV infected adults.

Dosage and Administration

Dosage: Adults

Videx EC capsules should be administered on an empty stomach. Videx EC capsules should be swallowed intact. The recommended daily dose is dependent on body weight and is administered as one capsule given on a once daily schedule as outlined in Table 1.

Table 1:

Patient Baseline Weight	**VIDEX EC capsules**
< 60kg	250mg OD
≥ 60kg	400mg OD

Adult Patients with Renal Impairment:

In adult patients with impaired renal function, the dose of **Videx EC** should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of **Videx EC** in adult patients with renal insufficiency are presented in Table 2.

Table 2. Recommended Dosage in patients with Renal impairment by Body Weight [a]

Creatinine Clearance (mL/min)	Dosage (mg)	
	At least 60kg	Less than 60kg
at least 60	400 once daily	250 once daily
30-59	200 once daily	125 once daily
10-29	125 once daily	125 once daily
Less than 10	125 once daily	[b]

[a] Based on studies using buffered formulation of didanosine
[b] Not suitable for use in patients less than 60kg with CL_{cr} less then 10mL/min.

For patients requiring CAPD or haemodialysis, follow dosing recommendations for patients with creatinine clearance less than 10mL/min, shown in Table 2. It is not necessary to administer a supplemental dose of didanosine following haemodialysis.

Contraindications

Videx EC is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to didanosine or any of the components of the formulations.

Warnings

The major clinical toxicities of **Videx EC** are pancreatitis and peripheral neuropathy.

1. Pancreatitis

Fatal and nonfatal pancreatitis has occurred during therapy with didanosine **used alone or in combination regimens in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. Videx EC should be suspended in patients with signs or symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis. Patients treated with Videx EC in combination with stavudine, with or without hydroxyurea, may be at increased risk of pancreatitis.** When treatment with other medicines known to cause pancreatic toxicity is required (for example, IV pentamidine) or known to increase exposure or activity of didanosine (eg hydroxyurea or allopurinol), suspension of **Videx EC** is recommended. Allopurinol was observed to increase exposure to didanosine in renally impaired patients and healthy volunteers and may increase the risk of dose-related toxicities such as pancreatitis. It is recommended that these two drugs not be administered together.

The incidence of pancreatitis and potential manifestations of pancreatitis in the adult phase 1 studies with patients entered at oral doses ≤ 12.5 mg/kg/day (an average daily dose similar to that expected from the recommended dosage) were: Pancreatitis (9%), abdominal pain (10%), increase amylase (18%) and abdominal pain together with increased amylase (7%).

In the Expanded Access Programme for didanosine, where the median duration of exposure was shorter than in the phase 1 studies (5 months versus 8.5 months), lower incidences of pancreatitis (abdominal pain 5%, increased amylase 8%) were reported. For 27 patients treated with didanosine who had a history of pancreatitis, 8 (30%) developed pancreatitis. Fatal pancreatitis occurred in 27 of 7806 treated patients (0.35%).

Positive relationships have been found between risk of pancreatitis and steady state plasma concentration of didanosine, as well as with daily oral dose. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment. Patients with a history of pancreatitis should be followed more closely, as should those with other risk factors such as diagnosis of AIDS, CD4 cell counts below 100 cells/μL, and risk factors for pancreatitis in general, such as alcohol consumption and elevated triglycerides.

Videx EC should be used with extreme caution and only if clearly indicated in patients with risk factors for pancreatitis. For example the following patients may be at increased risk for developing pancreatitis and should be followed closely for signs and symptoms of pancreatitis: patients with advanced HIV infection, patients with a history of pancreatitis, elderly patients, and patients with renal impairment if treated with unadjusted doses.

If symptoms of pancreatitis occur (See 'Adverse Effects'), **Videx EC** therapy should be suspended until resolution of symptoms.

In paediatric studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses below 300 mg/m^2/day and in 5 of 38 (13%) of patients treated at higher doses. In paediatric patients with symptoms similar to those described above, didanosine use should be suspended until the diagnosis of pancreatitis is excluded.

2. Peripheral Neuropathy

Patients with a history of peripheral neuropathy or those receiving **Videx EC** in combination with other neurotoxic drugs may be at increased risk of developing peripheral neuropathy. These patients should be carefully monitored. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-patients receiving hydroxyurea in combination with antiretroviral agents including didanosine, with or without stavudine.

Discontinuation of **Videx EC** should be considered in patients who develop peripheral neuropathy.

Peripheral neuropathy occurred in 34% of patients in phase 1 studies treated with didanosine doses at or below the currently recommended dose. Patients should be monitored for the development of a neuropathy that is usually characterised by distal numbness, tingling, or pain in the feet or hands.

In the Expanded Access Programme, where the median duration of exposure to didanosine was shorter than in the adult phase 1 studies, the incidence of neuropathy was 16%.

Neuropathy occurred more frequently in patients with a history of neuropathy or neurotoxic medicine therapy. These patients may be at increased risk of neuropathy during didanosine therapy.

Neuropathy has been reported rarely in children treated with didanosine. However, because signs and symptoms of neuropathy are difficult to assess in children, physicians should be alerted to the possibility of this event.

3. Liver Disease and Liver Failure

Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with antiretroviral agents in combination with hydroxyurea. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. This combination should be avoided.

The safety and efficacy of **Videx EC** have not been established in patients with significant underlying liver disorders. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, 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. Liver failure of unknown etiology has occurred in less than 0.2% of patients receiving didanosine.

4. Retinal Depigmentation and Vision

Retinal changes and optic neuritis have been reported in patients taking didanosine. Periodic retinal examinations should be considered for patients receiving **Videx EC.**

Paediatric patients receiving **Videx EC** have demonstrated retinal or optic nerve changes on rare occasions, particularly at doses above those recommended. Four paediatric patients demonstrated retinal depigmentation at doses of didanosine above 300 mg/m^2/day. Until further information is available from ongoing clinical trials with children treated at currently recommended lower doses of didanosine, it has been proposed that children receiving didanosine should undergo dilated retinal examination every 6 months or if a change in vision occurs. (See "**Adverse Reactions**").

5. Lactic Acidosis/ Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretovirals. Treatment with nucleoside analogues should be discontinued in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology.

A majority of these cases have been in women. Obesity and prolonged nucleotide exposure may be a risk factor. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk. Particular caution should be exercised when administering **Videx EC** to any patient with known risk factors for liver disease; however cases have also been reported in patients with no known risk factors. Treatment with **Videx EC** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.

6. Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including **Videx EC**. In patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to indolent or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (PCP). Any inflammatory symptoms should be elevated, 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.

7. Fat Redistribution

Redistribution/accumulation of body fat (lipodystrophy/lipoatrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and 'cushingoid appearance" have been observed in patients receiving antiretroviral therapy.

8. Non-cirrhotic Portal Hypertension

Postmarketing cases of non-cirrhotic portal hypertension have been reported, including cases leading to liver transplantation and death. Cases of didanosine-associated non-cirrhotic portal hypertension were confirmed by liver biopsy in patients with no evidence of viral hepatitis. Common presenting features included elevated liver enzymes oesophageal varices, haematemesis, ascites, and splenomegaly.

Patients receiving **Videx EC** 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 normalised ratio (INR) and ultrasonography should be considered. Videx should be discontinued in patients with evidence of non-cirrhotic portal hypertension.

Precautions

Ingestion of didanosine with food reduces the absorption of didanosine by as much as 50%. Therefore, **Videx EC** should be administered on an empty stomach.

Patients with Phenylketonuria:

Videx EC Capsules do not contain phenylalanine.

Adult Patients with Renal Impairment:

In adult patients with impaired renal function, the dose of **Videx EC** should be adjusted to compensate for the slower rate of elimination. See DOSAGE AND ADMINISTRATION for recommended doses and dosing intervals of **Videx EC** in adult patients with renal insufficiency.

Elderly Patients

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 Dosage and Admnistration**).

Patients with Hepatic Impairment:

Patients with hepatic impairment may be at greater risk for toxicity related to **Videx EC** treatment due to altered metabolism; a dose reduction may be necessary.

Hyperuricaemia:

Videx EC has been associated with asymptomatic hyperuricaemia; treatment suspension may be necessary if clinical measures aimed at reducing uric acid levels fail.

Myopathy:

Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were approximately 1.2 to 12 times the estimated human exposure. The relationship of this finding to the potential of didanosine to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of other nucleoside analogues.

Carcinogenesis and Mutagenesis:

Lifetime carcinogenicity studies were performed in mice and rats for 22 and 24 months, respectively. Mice were administered dietary didanosine 120, 800 or 1200mg/kg/day. Due to toxicity, the mid- and high-doses were lowered to 300 and 600 mg/kg/day, respectively, in week 20 in females and in week 36 in males, and were further reduced to 210 mg/kg/day in mid- and high-dose females in week 36. At the maximum tolerated doses of 120mg/kg/day in females and 300 mg/kg/day in males, systemic exposures were approximately 1.1 and 2.7 times, respectively, the clinical exposure ($AUC_{0\text{-}24h}$). Rats were administered dietary didanosine 100, 250 or 1000 mg/kg/day. The high-dose was reduced to 500 mg/kg/day after 18 months, due to toxicity. Systemic exposures in the 18^{th} month at the respective doses were approximately 0.59, 1.2 and 5.9 times the clinical exposure ($AUC_{0\text{-}24h}$). There was no evidence of carcinogenicity in either species at the maximally tolerated doses.

No evidence of mutagenicity (with or without metabolic activation) was observed in Ames Salmonella mutagenicity assays or in a mutagenitic assay conducted with Escherichia coli tester strain WP2 uvrA where only a slight increase in revertants was observed with Videx.

In a mammalian cell gene mutation assay conducted in L5178Y/TK +/- mouse lymphoma cells, didanosine was weakly positive both in the absence and presence of metabolic activation at concentrations of approximately 2000 μg/mL and above. In an in vitro cytogenic study performed in cultured human peripheral lymphocytes, high concentrations of didanosine (>500 μg/mL) elevated the frequency of cells bearing chromosome aberrations. Another in vitro mammalian cell chromosome aberration study using Chinese Hamster Lung cells revealed that didanosine produces chromosome aberrations at >500 μg/mL after 48 hours of exposure. However, no significant elevations in the frequency of cells with chromosome aberrations were seen at didanosine concentrations up to 250 μg/mL. Similar chromosomal aberation effects were induced by the natural nucleoside of didanosine (2'-deoxyinosine), suggesting that these effects of didanosine were not due to a direct genotoxic interaction. In a BALB/c 3T3 in vitro transformation assay, didanosine was considered positive only at concentrations of 3000 μg/mL and above, whereas deoxyinosine induced a positive response in this assay at 1000 μg/mL and above. No evidence of genotoxicity was observed in rat and mouse micronucleus assays. The rats received oral didanosine (up to

100mg/kg/day) for 7 days. The mice received oral didanosine (up to 1000mg/kg/day) for 4 weeks or intravenous didanosine (up to 250mg/kg/day) for 4 days.

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

Pregnancy, Reproduction and Fertility:

Pregnancy Category: B2

Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the foetus due to didanosine. At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains but the physical and functional developments of the offspring was not impaired and there were no major changes in the F2 generation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.

Nursing Mothers:

It not known whether **Videx EC** is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions from **Videx EC** in nursing infants, mothers should be instructed to discontinue nursing when taking **Videx EC**.

Effects on ability to drive and to use machines

The effect of Videx EC on driving and operating machinery has not been studied.

ADVERSE EFFECTS

The major toxicities of **Videx EC** are pancreatitis and peripheral neuropathy (see "**Warnings**").

A serious toxicity of **Videx EC** is pancreatitis. Pancreatitis resulting in death has been observed in patients who received **Videx EC** alone or in combination regimens (including combinations that contain stavudine) in controlled clinical trials and in spontaneous reports.

Patients treated with Videx in combination with stavudine may be at increased risk for pancreatitis. (See "**Warnings**")

Other important toxicities include lactic acidosis and severe hepatomegaly with steatosis, retinal changes and optical neuritis and peripheral neuropathy.

When **Videx EC** is used in combination with other agents with similar toxicities, the incidences of these toxicities may be higher than when **Videx EC** is used alone. Thus, patients treated with combination regimens including stavudine may be at increased risk for liver function abnormalities (see "**Warnings**") and peripheral neuropathy (see "**Warnings**").

Patients receiving **Videx EC** may develop peripheral neuropathy, usually characterized by bilateral symmetrical distal numbness, tingling, and pain in feet and, less frequently, hands. In clinical trials, the frequency appeared to be related to dose and/or stage of disease; lower rates were seen in patients with less advanced disease. In controlled clinical trials, neuropathy has occurred more frequently in patients with a history of neuropathy or concomitant use of neurotoxic drug therapy, including stavudine.

Adults:
The most frequent adverse event in uncontrolled trials was diarrhoea, reported in 18% of the patients and classified as serious in 1.9% of reported cases.

Other adverse events, reported in 2% or more of all patients in uncontrolled trials include: nausea/vomiting (8%), chills/fever (5%), headache (5%), pain (4%), abdominal pain (5%), rash/pruritus (4%), asthenia (3%), seizure/convulsions (3%), pneumonia (2%), infection (2%), confusion (2%), and insomnia (2%).

CNS depression, constipation, stomatitis, myalgia, arthritis, taste disturbance, dry mouth, alopecia, and dizziness have also been reported. Other gastrointestinal, metabolic/nutritional, nervous, musculoskeletal, respiratory, cardiovascular and urogenital system effects have been reported as have cutaneous and special sense organ effects.

Liver failure of unknown etiology has occurred rarely in patients taking **didanosine**.

In a controlled clinical trial that compared VIDEX administered OD in combination with stavudine BID and nelfinavir TID with the combination of zidovudine TID, lamivudine BID and nelfinavir TID there were no differences in rates of premature discontinuation from study therapy or in the incidence of adverse events between the two treatment groups. The types of adverse events reported were similar to those reported in other clinical studies using the individual drugs. Limited data indicated that VIDEX given OD exhibits a similar safety profile as VIDEX given BID.

Hyperuricaemia has been associated with **didanosine** therapy. Other clinically significant laboratory abnormalities reported include: leucopenia, thrombocytopenia, anaemia, and changes in bilirubin, alkaline phosphatase, SGOT, SGPT, and amylase. The relationship to therapy of these observations has not been established.

In a controlled clinical trial that compared VIDEX administered OD in combination with stavudine OD in combination with stavudine BID and nelfinavir TID with the combination of zidovudine TID, lamivudine BID abd nelfinavir TID, serious laboratory test abnormalities were generally similar to those reported in other controlled clinical trials. Serious laboratory abnormalities reported with both of these regimens were generally similar to those reported in patients treated with any of the individual drugs. Limited data indicated that VIDEX given OD exhibits a similar safety profile as VIDEX given BID.

Some events, especially gastrointestinal disturbances such as nausea and diarrhea, may be related to the buffer or antacid in Videx buffered formulations. The incidence of these events attributable to **Videx EC** (which does not contain buffers) in combination regimens has not been defined.

Postmarketing Experience

The following events have been identified during post approval of Videx. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, or causal connection to didanosine, or a combination of these factors.

Body as a Whole – alopecia, anaphylactoid reaction, asthenia, chills/fever, and pain
Digestive Disorders – anorexia, dyspepsia and flatulence.
Exocrine Gland Disorders – pancreatitis (including fatal cases), sialoadenitis, parotid gland enlargement, dry mouth and dry eyes.
Haematologic Disorders – anaemia, granulocytopenia, leucopenia, and thrombocytopenia
Liver – lactic acidosis and hepatic steatosis; non-cirrhotic portal hypertension (See WARNINGS), hepatitis and liver failure
Metabolic Disorders – diabetes mellitus, elevated serum alkaline phosphatase level, elevated serum amylase level, hypoglycaemia and hyperglycaemia
Musculoskeletal Disorders – myalgia (with or without increases in creatinine kinase), rhabdomyolysis including acute renal failure and haemodialysis, arthralgia and myopathy)
Ophthalmologic Disorders – retinal depigmentation and optic neuritis.

Interactions

Co-administration of **Videx EC** with drugs that are known to cause peripheral neuropathy or pancreatitis may increase the risk of these toxicities. Patients who receive these drugs should be carefully observed. Neuropathy has occurred more frequently in patients with a history of neuropathy or neurotoxic drug therapy and these patients may be at increased risk of neuropathy during **Videx EC** therapy (see Adverse Effects).

Allopurinol.
When didanosine was coadministered with allopurinol in two patients with renal impairment (creatinine clearance 15-18mL/min), the AUC of didanosine increased approximately 4-fold. In 14 healthy volunteers, the mean AUC of didanosine increased approximately 2-fold when given with allopurinol. Thus, the risk of dose-related toxicities, such as pancreatitis, may be increased if didanosine and allopurinol are administered together. It is recommended that these two drugs are not to be administered.

Methadone:
Patients should be closely monitored for adequate clinical response when **Videx EC** is coadministered with methadone, including monitoring for changes in HIV RNA viral load.

Tenofovir disoproxil fumarate.
Exposure to **Videx EC** is increased when coadministered with tenofovir, therefore a dose reduction of **Videx EC** is recommended. Please also refer to the tenofovir prescribing information for further details on drug-interactions and precautions.

All patients receiving tenofovir disoproxil fumarate and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response. **Videx EC** should be suspended if signs and symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop. Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate at a dose of 400mg daily.

Zidovudine.
Combination studies of **Videx** (up to 500mg/day) and zidovudine (up to 600mg/day) have not revealed any unexpected toxicities. These studies demonstrated improvement in virological and immunological markers.

Specific drug interaction studies have been conducted between **Videx EC** capsules and ciprofloxacin, indinavir and ketoconazole without evidence of interaction.

Delavirdine: When didanosine was co-administered with delavirdine there was a decrease of approximately 20% in the AUC for both didanosine and delavirdine, relative to when administration was separated by at least 1 hour. Administration of didanosine and delavirdine should be separated by 1 hour.

Ribavirin: Exposure to didanosine or its inactive metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities. Co-administration of dianosine and ribavirin is not recommended. There have been reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactactemia/lactic acidosis.

Indinavir: Indinavir and Videx tablets should be administered at least one hour apart on an empty stomach. Indinavir may need an acidic pH for optimum absorption whereas didianosine is degraded by acid; Videx tablets are buffered to increase the gastric pH. There is no drug-drug interaction between Videx EC capsules and indinavir.

Specific drug interaction studies have been conducted between Videx tablet formulations and zidovudine, stavudine, ranitidine, loperamide, metoclopramide, foscarnet, trimethoprim, sulfamethoxazole, dapsone and rifabutin without evidence of interaction.

Use with Stavudine- and Hydroxyurea-based regimens.
When didanosine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when didanosine is used alone. This, patents treated with **Videx EC** in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and sever peripheral neuropathy (see WARNINGS). The combination of **Videx EC** and hydroxyurea, with or without stavudine, should be avoided.

Drugs whose absorption can be affected by the level of acidity in the stomach: **Videx EC** capsules may be given simultaneously with agents such as ketoconcazole and itraconazole, since gastric acidity is not affected by this didanosine formulation. Videx buffered formulations should be administered at least two hours after drugs such as ketoconazole or itraconazole.

A study in 4 patients revealed that concomitant administration of ganciclovir does not significantly affect the pharmacokinetics of **Videx**. There is no evidence that Videx potentiates the myelosuppressive effects of ganciclovir.

As with other products containing magnesium antacid components, **Videx** Chewable/Dispersible Buffered Tablets should not be administered with a prescription antibiotic containing any form of tetracycline.

Plasma concentrations of some quinolone antibacterials are decreased when administered with antacids containing magnesium or aluminium. Therefore, doses of quinolone antibacterials should not be administered within 2 hours of taking **Videx**. Concomitant administration of antacids containing magnesium or aluminium with **Videx** tablets or powder may potentiate adverse effects associated with the antacid components.

Overdosage

There is no known antidote for **Videx EC** (**didanosine**) overdosage. Experience in the phase 1 studies in which didanosine was initially administered at doses ten times the currently recommended dose indicates that the complications of chronic overdosage would include pancreatitis, peripheral neuropathy, diarrhoea, hyperuricaemia or, possible, 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 amount present in the body at the start of dialysis).

Pharmaceutical Precautions

Didanosine is unstable in acidic solutions. For example, at pH <3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes. The didanosine contained within the beadlets of **VIDEX EC** capsules is protected against gastric acid by an enteric coating, which dissolves when the beadlets empty into the higher pH of the small intestine, the site of drug absorption.

Videx EC Capsules
The capsules should be stored in tightly closed bottles*, or in the blister packing at below 25^0C.

* **Videx EC** in blister packs is not marketed

Medicine Classification

Prescription Medicine.

Package Quantities

Videx EC Capsules: 125mg, 200mg, 250mg and 400mg, 30s.

Further Information

Information for Patients:

Videx EC is not a cure for HIV infection, and patients may continue to acquire illnesses associated with AIDS or ARC, including opportunistic infection. **Videx EC** has not been shown to reduce the incidence or frequency of such illnesses. Therefore, patients should remain under care of a physician when using **Videx EC**.

Patients should be informed that the major toxicities of **Videx EC** are pancreatitis, which has been fatal in some patients, and peripheral neuropathy. Symptoms of pancreatitis include abdominal pain, nausea and vomiting. Symptoms of peripheral neuropathy include tingling, burning, pain or numbness in the hands or feet. Patients should be advised that these symptoms should be reported to their physicians. They should be counseled that these toxicities occur with greatest frequency in patients with a history of these events, and that dose modification and/or discontinuation of **Videx EC** may be required if toxicity develops. They should be cautioned about the use of other medications that may exacerbate the **Videx EC** toxicity, including alcohol.

Patients should be told that the long-term effects of **Videx EC** are unknown at this time. Patients should be advised that **Videx EC** therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inactive Ingredients:

Videx EC capsules contain sodium starch glycolate, sodium carboxymethylcellulose, methacrylic acid copolymer, diethyl phthalate, talc, sodium hydroxide, gelatin, titanium dioxide, silicon dioxide and sodium lauryl sulphate.

Sodium content of Videx EC capsules:
Sodium content is minimal : 0.53 mg for the 125-mg capsule, 0.85mg for the 200mg capsule, 1.06 mg for the 250mg capsule and 1.7mg for the 400mg capsule.

Cytotoxicity:
The results of cytotoxicity studies in various cell lines have shown little cytotoxic action with didanosine. In cultured human bone marrow progenitor cells, the concentration of medicine necessary to inhibit cell growth 50% (IC_{50}) was > 100 μM for didanosine. For zidovudine, IC_{50} values under similar assay conditions ranged from 0.13 to 5 μM.

Method of Preparation

Videx EC Capsules
Videx EC Capsules should be swallowed intact. Studies evaluating the stability of the beadlets outside the capsules have not been completed. The recommended daily dose is dependent on body weight and is usually administered as one capsule.

Name and Address

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