Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hivid 0.375 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 0.375 mg zalcitabine.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.
Oval-shaped film-coated tablets of beige to reddish grey colour with ‘HIVID 0.375’ printed on one side and ‘ROCHE’ on the other side with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

HIVID (zalcitabine) is indicated in HIV-infected adults in combination with other antiretroviral drugs (see section 5.1).

4.2 Posology and method of adminstration

Recommended dosage
The recommended daily dose of HIVID in combination with other antiretroviral drugs is 0.75 mg administered every 8 hours (2.25 mg total daily dose). Since systemic exposure decreases only slightly with food HIVID may be administered with and without food. The dosage schedule of any other antiretroviral drug should be prescribed as recommended in the complete Product Information for these drugs.

Monitoring of patients
Periodic complete blood counts clinical chemistry tests should be performed. Serum amylase levels should be monitored in those individuals who have a history of elevated amylase, pancreatitis, ethanol abuse, who are on parenteral nutrition or who are otherwise at high risk of pancreatitis. Careful monitoring for signs or symptoms suggestive of peripheral neuropathy is recommended, particularly in individuals with a low CD_4 cell count who are at a greater risk of developing peripheral neuropathy while on therapy (see section 4.4).

Dose adjustment in particular clinical situations

Renal impairment:
Based on sparse data dose adjustment in patients with *renal impairment* should be considered as follows: estimated creatinine clearance 10 to 40 ml/min - reduce the HIVID dose to 0.750 mg every 12 hours; estimated creatinine clearance <10 ml/min - reduce the HIVID dose to 0.750 mg once a day.

Hepatic impairment*:*
Recommendations for dose adjustment cannot be given for patients with hepatic impairment because of limited experience (see section 5.2).

Children
Recommendations for the dosage in children younger than 13 years cannot be given since the experience in this age group is limited.

Dosage adjustment in case of undesirable effects during combination therapy
For toxicities that are likely to be associated with HIVID (e.g. peripheral neuropathy, severe oral or oesophageal ulcers, pancreatitis, elevated liver function tests especially in patients with chronic hepatitis B), the HIVID dose should be reduced or HIVID should be interrupted or discontinued as appropriate (see section 4.4). For recipients of combination therapy with HIVID and other antiretroviral agents, dose adjustments or interruption for each drug should be based on the known toxicity profile of the individual drugs. See the complete Product Information for each drug used in combination for a description of known drug associated adverse reactions.

4.3 Contraindications

HIVID is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

Peripheral neuropathy

The major clinical toxicity of HIVID is peripheral neuropathy. HIVID-related peripheral neuropathy is a sensorimotor neuropathy characterized initially by numbness and burning dysaesthesia involving the distal extremities. These symptoms may be followed by sharp shooting pains or severe continuous burning pain if the drug is not withdrawn. The neuropathy may progress to severe pain requiring narcotic analgesics and is potentially irreversible, especially if HIVID is not stopped promptly. In some patients, symptoms of neuropathy may initially progress despite discontinuation of HIVID. With prompt discontinuation of HIVID, the neuropathy is usually slowly reversible.

Patients with moderate to severe peripheral neuropathy, as evidenced by symptoms accompanied by objective findings, are advised to avoid HIVID.

HIVID should be used with caution in patients with a risk of developing peripheral neuropathy: patients with low CD_4 cell counts ($CD_4 < 50$ cells/mm^3) and/ or patients receiving HIVID concomitantly with drugs that have the potential to cause peripheral neuropathy (see section 4.5). Careful monitoring is strongly recommended for these individuals. If peripheral neuropathy occurs in patients treated with HIVID, the drug should be interrupted or discontinued.

Pancreatitis

Fatal pancreatitis has been observed with the administration of HIVID. Pancreatitis and asymptomatic elevated serum amylase are uncommon occurrences during HIVID therapy.
Caution should be exercised when administering HIVID to any patient with a history of pancreatitis or known risk factor for the development of pancreatitis.
Patients with a history of pancreatitis or a history of elevated serum amylase should be followed more closely while on HIVID therapy. Treatment with HIVID should be interrupted in the setting of a rising serum amylase level associated with dysglycaemia, rising triglyceride level, decreasing serum calcium or other parameters suggestive of impending pancreatitis, until a clinical diagnosis is reached. Treatment with HIVID should also be interrupted if treatment with another drug known to cause pancreatitis (e.g. pentamidine) is required (see also section 4.5).
HIVID should be restarted only after pancreatitis has been ruled out. If clinical pancreatitis develops during HIVID administration, it is recommended that HIVID be permanently discontinued.

Other severe undesirable effects

Lactic acidosis: lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) 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 and renal failure.
Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
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 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. Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons.
Cases of hepatic failure in association with underlying hepatitis B and HIVID monotherapy have been reported
Patients at increased risk should be followed closely (see also section 4.6).

Infrequent cases of oral and esophageal ulcer have been reported in individuals receiving HIVID therapy. Patients with esophageal ulcer should stop zalcitabine therapy until causality is established (opportunistic pathogens; medical agents). Infrequent cases of hypersensitivity reactions (anaphylactic reaction, urticaria without other signs of anaphylaxis) have also been reported.
Infrequent cases of cardiomyopathy and congestive heart failure have been reported in patients receiving HIVID.
Treatment with HIVID in patients with baseline cardiomyopathy or history of congestive heart failure should be approached with caution.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8 Undesirable effects).

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 (anaemia, 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 child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, 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.

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 carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Particular clinical situations

Renal impairment
For patients with renal impairment dose adjustment should be considered (see section 4.2)

Liver disease
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.

In individuals with preexisting liver disease or with a history of ethanol abuse, the use of HIVID may be associated with exacerbation of hepatic dysfunction.

Paediatric use
Safety and efficacy of HIVID therapy in HIV-infected children younger than 13 years of age has not been established.

Elderly patients
Specific information about the use of zalcitabine in the elderly is not available. In such patients special attention should be paid to renal and hepatic function information.

Lactose
HIVID contains lactose. Therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Information for patients

Patients should be informed that HIVID is not a cure for HIV infection, that they may continue to develop illnesses associated with advanced HIV infection including opportunistic infections. Since it is frequently difficult to determine whether symptoms are a result of drug effect or underlying disease manifestation, patients should be encouraged to report all changes in their condition to their physician. Patients should be informed that the use of HIVID or other antiretroviral drugs do not preclude the ongoing need to maintain practices designed to prevent transmission of HIV. Patients should be advised of the early symptoms of peripheral neuropathy and pancreatitis and should be instructed to promptly report them to their physician. Since the development of peripheral neuropathy appears to be dose-related to HIVID, patients should follow their physicians' instructions regarding the prescribed dose. Women of childbearing age should use effective contraception while using HIVID.

4.5 Interaction with other medicinal products and other forms of interaction

Nucleoside reverse transcriptase inhibitors
Zalcitabine has no significant effect on the intracellular phosphorylation of **zidovudine**, as shown *in vitro*. In the same study it was shown that **didanosine** and **stavudine** had no significant effect on the intracellular phosphorylation of **zalcitabine**.
In vitro studies revealed that **lamivudine** significantly inhibited intracellular **zalcitabine** phosphorylation in a dose dependent manner. Effects were already seen with concentrations corresponding to therapeutic plasma levels in humans.
At concentrations exceeding clinically relevant plasma levels **zalcitabine** also decreases **lamivudine** phosphorylation. Concomitant use of **zalcitabine** and **lamivudine** is therefore not recommended.

HIV-1 proteinase inhibitors
There is no pharmacokinetic interaction between saquinavir and HIVID. No formal interaction trials with HIVID and proteinase inhibitors other than saquinavir have been conducted. As zalcitabine is mainly excreted as unchanged drug

in the urine, there is no rationale to expect an influence of other proteinase inhibitors on the plasma levels of zalcitabine.

Drugs that have the potential to cause peripheral neuropathy
HIVID should be used with caution in patients receiving other medications, which have the potential to cause peripheral neuropathy (see section 4.4). Drugs which have been associated with peripheral neuropathy include antiretroviral nucleoside analogues, chloramphenicol, cisplatin, dapsone, disulfiram, ethionamide, glutethimide, gold, hydralazine, iodoquinol, isoniazid, metronidazole, nitrofurantoin, phenytoin, ribavirin and vincristine.
Drugs such as amphotericin, foscarnet and aminoglycosides may increase the risk of developing peripheral neuropathy or other HIVID-associated adverse events by interfering with the renal clearance of zalcitabine (and thereby raising systemic exposure). Patients who require the use of one of these drugs with HIVID should have frequent clinical and laboratory monitoring with dosage adjustment for any significant change in renal function.

Drugs that have the potential to cause pancreatitis
Treatment with HIVID should be interrupted, when the use of a drug that has the potential to cause pancreatitis is required. One death due to fulminant pancreatitis possibly related to HIVID and intravenous pentamidine was reported. If pentamidine is required to treat pneumocystis carinii pneumonia, treatment with HIVID should be interrupted (see section 4.4).

Probenecid / cimetidine / trimethoprim
Concomitant administration of probenecid, cimetidine or trimethoprim decreases the elimination of zalcitabine, most likely by inhibition of renal tubular secretion of zalcitabine. Patients receiving these drugs in combination with zalcitabine should be monitored for signs of toxicity and the dose of zalcitabine reduced if warranted.

Antacid products
Absorption of zalcitabine is moderately reduced (approximately 25%) when coadministered with magnesium/aluminium containing antacid products. The clinical significance of this reduction is not known, hence zalcitabine is not recommended to be ingested simultaneously with magnesium/aluminium containing antacids.

Metoclopramide
Bioavailability is mildly reduced (approximately 10%) when zalcitabine and metoclopramide are coadministered.

Ribavirin
When combined with ribavirin the antiretroviral activity of zalcitabine was impaired under *in vitro* conditions.

4.6 Pregnancy and lactation

Use during pregnancy
The safety of HIVID for use in human pregnancy has not been established. A limited number of birth defects were reported for *in utero* Hivid-exposed neonates, but since different antiretroviral drugs were taken concomitantly, the contribution of zalcitabine cannot be assessed properly. A teratogenic effect has been observed in animals at very high exposures to zalcitabine (see section 5.3). Neurological and behavioural abnormalities have been observed during foetal development and lactation in offspring of rats treated with zalcitabine for which a no-effect dose was not determined. Therefore HIVID should only be used during pregnancy if the expected benefit justifies the possible risk to the child. Fertile women should not receive HIVID unless they are using effective contraception during the therapy period.

Use during lactation
It is not known whether zalcitabine is excreted in human milk. Women receiving zalcitabine should not breast feed their infants. HIV infected women should not breast feed their infants in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

There is no clinical evidence that HIVID may alter the patient's ability to drive or use machines. However, the adverse event profile should be taken into account.

4.8 Undesirable effects

The major undesirable effect of HIVID is peripheral neuropathy. It has been reported with a frequency of more than 40 % in clinical studies and is mainly expressed as hypoesthesia, paraesthesia or pain in the lower and upper extremities. Prompt discontinuation of Hivid treatment is recommended due to potential irreversibility (see section 4.4). Other frequent adverse events observed in Hivid monotherapy trials include headache, rash, fatigue, nausea, ulcerative stomatitis and myalgia.

Although Hivid is currently approved for the use in antiretroviral combination therapy only, the undesirable effects observed in a monotherapy trial are presented in the table below since they are more suitable for attributing a certain adverse event to the medicinal product. However, individual undesirable effects are unchanged during combination therapy.

The percentage of the 320 patients taking Hivid as monotherapy in the double-blind study N3300 that experienced adverse drug reactions (considered to be at least remotely related to Hivid by the investigator) with a frequency of equal to or higher than 1% in the zalcitabine monotherapy arm are listed in Table 1 below.

Table 1. Adverse reactions that occurred in equal to or more than 1% of patients taking zalcitabine in N3300

Body system Adverse event	**Zalcitabine arm** N=320
Infections and infestations	
Pharyngitis	5.3%
Metabolism and nutrition disorders	
Anorexia	8.4%
Psychiatric disorders	
Confusion	2.8%
Depression	1.3%
Insomnia	1.3%
Nervous system disorders	
Peripheral neuropathy (see precautions section)	41.6%
- Hypoesthesia in lower and upper extremities	30.6%
- Paraesthesia in lower and upper extremities	30.7%
- Pain in lower and upper extremities	25.1%
- Weakness in lower and upper extremities	13.5%
- Reflexes decreased	3.4%
- Neuropathy	2.8%
- Decreased sensation	2.8%
- Hypoesthesia	2.8%
- Gait abnormal	1.9%
- Sensory disturbance	1.9%
- Absent Achilles tendon reflex	1.3%
Headache	17.8%
Dizziness	5.0%
Concentration impaired	1.6%
Eye disorders	
Hypoesthesia	2.8%
Xerophthalmia	1.3%
Cardiac disorders	
Heart racing	1.3%
Respiratory, thoraic and mediastinal disorders	
Coughing	4.1%
Dyspnea	2.2%

Body system Adverse event	**Zalcitabine arm** N=320
Gastrointestinal disorders	
Nausea	13.1%
Stomatitis ulcerative	12.8%
Diarrhoea	7.5%
Mouth dry	5.0%
Vomiting	6.9%
Dysphagia	4.7%
Abdominal pain	5.9%
Stomatitis aphthous	3.8%
Constipation	1.9%
Dyspepsia	1.9%
Glossitis	1.9%
Esophageal pain	1.9%
Esophageal ulcer (see precautions section)	1.9%
Stomatitis	1.6%
Skin and subcutaneous tissue disorders	
Rash	15.6%
Pruritus	9.4%
Night sweats	3.4%
Dermatitis	2.2%
Musculoskeletal, connective tissue and bone disorders	
Myalgia	12.2%
Arthralgia	3.8%
Pain feet	1.6%
Stiff neck	1.6%
Back pain	1.3%
General disorders and administration site conditions	
Fatigue	15.0%
Fever	6.5%
Pain	2.5%
Rigors	2.5%
Chest pain	1.9%
Investigations	
Weight decreased	6.6%

Marked laboratory abnormalities (grade III and IV) that occurred in more than 1% of the patients in the zalcitabine arm of study N3300 are presented in Table 2 below.

Table 2. Laboratory abnormalities

Laboratory abnormality	**Zalcitabine arm** N=320
SGPT increased	8.2%
Low absolute neutrophil count	5.8%
High absolute eosinophil count	5.8%
SGOT increased	5.6%
Low haemoglobin	3.8%
Low platelets	3.8%
Low white blood cell count	3.1%
Alkaline phosphatase increased	2.8%
Total bilirubin increased	2.2%
Creatinine increased	1.9%
WBC in urine	1.9%
High calcium	1.9%
High phosphorus	1.8%

The safety profile observed in three other controlled studies that contained a zalcitabine monotherapy arm (study NV14256 (n=325 patients taking zalcitabine), CPCRA002 (n=237 patients taking zalcitabine) and ACTG 155 (n=285 patients taking zalcitabine)), is generally in line with the safety findings described before.

Frequencies of
- additional relevant adverse drug reactions from other studies in which Hivid was used as mono- or combination therapy and
- adverse drug reactions/laboratory abnormalities that were reported with a significantly higher rate in Hivid monotherapy studies other than N3300

are given below.

The frequency of the adverse drug reactions is described using the following convention:

Very common	> 10%
Common	1% - 10%
Uncommon	0.1% - 1%
Rare	0.01% - 0.1%
Very rare	< 0.01% (including isolated reports)

In addition, events reported during post-marketing experience are presented. However, frequencies cannot be calculated from data generated outside clinical trials.

Immune system disorders
- post-marketing: hypersensitivity reactions

Metabolism and nutrition disorders
- rare: gout
- post-marketing: lactic acidosis

Psychiatric disorders
- common: anxiety
- uncommon: agitation, depersonalization, nervousness, amnesia, emotional lability, manic reaction
- rare: dementia, euphoria, somnolence

Nervous system disorders
- common: convulsions
- uncommon: neuritis, ataxia, hyperkinesia, taste perversion, tremor
- rare: abnormal coordination, Bell's palsy, dysphonia, hypertonia, hypokinesia, loss of taste, migraine, parosmia, stupor, syncope

Eye disorders
- uncommon: eye pain, eye abnormalities
- rare: abnormal vision

Ear and labyrinth disorders
- uncommon: deafness, vertigo
- rare: ear blockage, tinnitus

Cardiac disorders
- uncommon: cyanosis
- rare: atrial fibrillation, palpitation
- post-marketing: cardiomyopathy, congestive heart failure

Vascular disorders
- uncommon: flushing
- rare: cold extremities, hypertension

Gastrointestinal disorders
- common: flatulence, melena
- uncommon: pancreatitis (see section 4.4), distended abdomen, gum disorder, hemorrhoids, rectal hemorrhage, tongue ulceration, esophagitis, glossitis
- rare: eructation, gastritis, gastrointestinal hemorrhage, rectal ulcers, salivary gland enlargement

Hepato-biliary disorders
- common: abnormal hepatic function
- uncommon: hepatitis
- rare: hepatocellular damage, jaundice
- post-marketing: hepatic failure, hepatomegaly, hepatic steatosis

Skin and subcutaneous tissue disorders
- uncommon: erythematous papules, alopecia, urticaria
- rare: acne, bullous eruptions

Musculoskeletal, connective tissue and bone disorders
- common: musculoskeletal pain
- rare: arthritis, arthropathy, myositis, muscle weakness, twitching

Renal and urinary disorders
- uncommon: micturition frequency, abnormal renal function, renal cyst, polyuria
- rare: acute renal failure, renal calculus, toxic nephropathy

General disorders and administration site conditions
- very common: fever
- common: asthenia
- uncommon: malaise
- rare: edema, neuralgia

Laboratory abnormalities
- very common: neutropenia, anemia, low white blood cell count, SGPT increased, SGOT increased
- common: alkaline phosphatase increased, amylase increased, bilirubin increased, hypoglycemia, hyperglycemia, hyponatremia, hypophosphatemia, hypocalcemia, creatinine increased, elevated triglycerides
- uncommon: hyperuricemia

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia (see section 4.4).

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 (see section 4.4).

4.9 Overdose

Acute overdose
There is little experience with acute HIVID overdosage and the sequelae are unknown. There is no known antidote for HIVID overdosage. It is not known whether zalcitabine is dialysable by peritoneal dialysis or hemodialysis.

Chronic overdosage
In an initial dose-finding study in which zalcitabine was administered at doses 25 times (0.25 mg/kg every 8 hours) the currently recommended dose, one patient discontinued HIVID after one and one-half weeks of treatment subsequent to the development of a rash and fever. In the early phase I studies, all patients receiving HIVID approximately six times the current total daily recommended dose experienced peripheral neuropathy by week 10.
Eighty percent of the patients who received approximately two times the current total daily recommended dose experienced peripheral neuropathy by week 12.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral agent
ATC code: J05A F03

Virology
HIVID is an antiretroviral agent. HIVID has been shown *in vitro* to act additively or synergistically with zidovudine and saquinavir.

Mechanism of action
Zalcitabine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxycytidine, in which the 3'-hydroxyl group is replaced by hydrogen. Within cells, zalcitabine is converted to the active metabolite, dideoxycytidine 5'-triphosphate (ddCTP), by the sequential action of cellular enzymes. Dideoxycytidine 5'-triphosphate serves as an alternative substrate to deoxycytidine 5'-triphosphate (dCTP) for HIV reverse transcriptase. Inhibition of HIV replication is attained both by competing for utilization of the natural substrate and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and therefore the viral DNA growth is terminated.

Comparative studies of the antiviral activity of zalcitabine against HIV-1 and HIV-2 in vitro revealed no significant difference in sensitivity between the two viruses when activity was determined by measuring viral cytopathic effect. HIVID has been shown to reduce levels of HIV in infected individuals. A correlation has been established between the reduction of viral load and delay in disease progression and death.

Zalcitabine drug resistance
Current evidence demonstrates that the incidence of resistance to zalcitabine is an infrequent event which occurs late during therapy if combined with zidovudine. Specific phenotypic resistance to zalcitabine is usually associated with the appearance of a point mutation at codon 69 and was reported infrequently during zidovudine/zalcitabine combination therapy. Mutations at five individual codons of the reverse transcriptase gene have been associated with multidrug resistance, including zalcitabine, didanosine and zidovudine. These are A62V, V75I, F77L, F116Y and Q151M. Phenotypic cross-resistance of zalcitabine to zidovudine was never observed in clinical studies with concomitant use of zidovudine + zalcitabine in zidovudine naive patients.
However, in the presence of zidovudine sensitivity to zalcitabine might be reduced due to 215 point mutations ("multidrug resistance"). M41L/T215Y, K70R and T215Y viruses were resistant to zidovudine and sensitive to zalcitabine. 50% inhibitory concentration values for zalcitabine increased 5-fold with M41L/T215Y and T215Y viruses in the presence of zidovudine.

Prior exposure to didanosine, stavudine and lamivudine are reported to select genotypic changes at codons 65, 74, and 184 respectively. These mutations confer reduced sensitivity to zalcitabine in vitro.

There is no potential for cross resistance between zalcitabine and HIV protease inhibitors because of the different enzyme targets involved. The use of zalcitabine in combination with zidovudine plus the protease inhibitor saquinavir appears to delay the emergence of saquinavir resistance compared to the combination of only zidovudine plus saquinavir.

Clinical pharmacology
The efficacy of HIVID in combination with other antiretrovirals was mainly demonstrated in clinical endpoint studies where a double antiretroviral combination containing zalcitabine was compared to monotherapy. 4 large, randomised, double-blind trials combining HIVID with zidovudine or saquinavir (ACTG 175, Delta, CPCRA 007 and NV 14256) and activity data from 2 studies investigating HIVID in combination with saquinavir and/or zidovudine (ACTG 229 and NUCA 3002) were evaluated. Zalcitabine displayed in these trials, relatively to other antiretroviral substances, usually stronger effects on viral load than expectation based on CD_4^+ count would predict. Additional data are available from one further clinical endpoint study (CAESAR) investigating HIVID in combination with zidovudine+lamivudine±loviride, as well as data from a number of pilot studies evaluating HIVID in combination with other antiretrovirals, including other proteinase inhibitors and other non-nucleoside reverse transcriptase inhibitors.

Clinical Endpoint Studies
Studies ACTG 175, Delta and CPCRA 007 compared rates of disease progression and survival in HIV-1 infected patients treated with zidovudine 200 mg tid given as monotherapy or in combination with HIVID 0.750 mg tid. In these studies, the combination of zidovudine + HIVID was consistently superior to zidovudine monotherapy in terms of delayed disease progression and increased survival. The clinical benefits of zidovudine + HIVID appeared greatest in those patients with no or limited prior zidovudine experience.

NV 14256 was a double-blind study in which 940 patients were randomised to receive either saquinavir or HIVID or saquinavir + HIVID. Compared with saquinavir monotherapy, treatment with saquinavir + HIVID was associated with a 75% reduction in the risk of death (p=0.0001) as well as a 44% reduction in the combined endpoint of progression to AIDS or death (p=0.0043).

Additional Supportive Data
Clinical or activity marker benefit was observed in triple therapy regimens comprising HIVID in combination with zidovudine+saquinavir (ACTG 229), zidovudine+lamivudine±loviride (CAESAR), and zidovudine+ritonavir (M94-208).

5.2 Pharmacokinetic properties

The pharmacokinetics of zalcitabine have been evaluated in studies with HIV-infected patients following 0.01 mg/kg, 0.03 mg/kg and 1.5 mg oral doses, and a 1.5 mg intravenous dose administered as a 1-hour infusion.
The relevance of drug plasma levels to antiretroviral therapy for zalcitabine is not established. Therefore, no specific recommendations with regard to target plasma levels can be made.

Absorption and bioavailability
Following oral administration to HIV-infected patients, the mean absolute bioavailability was >80% (range 23% to 125%, n=19). The absorption rate of a 1.5 mg oral dose of zalcitabine (n=20) was reduced when administered with food. This resulted in a 39% decrease in mean maximum plasma concentrations (C_{max}) from 25.2 ng/ml (range 11.6 to 37.5 ng/ml) to 15.5 ng/ml (range 9.1 to 23.7 ng/ml), and a twofold increase in time to achieve maximum plasma concentrations from a mean of 0.8 hours under fasting conditions to 1.6 hours when the drug was given with food. The mean extent of absorption (as reflected by AUC) was decreased by 14%. The clinical relevance of this decrease is unknown.

Distribution
The steady-state volume of distribution following i.v. administration of a 1.5 mg dose of zalcitabine averaged 0.534 (± 0.127) l/kg.

The drug was <4% bound to plasma proteins, indicating that drug interactions involving binding-site displacement are unlikely.

Cerebrospinal fluid obtained 2-3.5 hours following 0.06 mg/kg or 0.09 mg/kg i.v. infusion showed measurable concentrations of zalcitabine. The CSF to plasma concentration ratio ranged from 9-37% (mean 20%), demonstrating penetration of the drug through the blood-brain barrier.

Metabolism and elimination
Zalcitabine is phosphorylated intracellularly to zalcitabine triphosphate, the active substrate for HIV-reverse transcriptase. Concentrations of zalcitabine triphosphate are too low for quantitation following administration of therapeutic doses to humans.
Zalcitabine metabolism in humans has not been fully evaluated. Zalcitabine does not undergo a significant degree of metabolism by the liver. Renal excretion is the primary route of elimination, and accounted for approximately 70% of an orally administered, radiolabeled dose (i.e. total radioactivity) within 24 hours after dosing. The mean elimination half-life is 2 hours and generally ranges from 1-3 hours in individual patients. Total mean body clearance following an intravenous dose averages 285 ml/min. Less than 10% of a radiolabeled dose of zalcitabine appears in the faeces.
In patients with normal renal function, the pharmacokinetics of zalcitabine was not altered during three times daily multiple dosing. Accumulation of drug in plasma during this regimen was negligible.

Pharmacokinetics in special populations
Pharmacokinetics in patients with renal impairment
Results from patients with renal impairment (estimated CrCl <55 ml/min) indicate that the half-life was prolonged (up to 8.5 hours) in these patients compared to those with normal renal function. Maximum plasma concentrations were higher in some patients after single dose.

Pharmacokinetics in patients with hepatic impairment
As zalcitabine is eliminated predominantly renal, pharmacokinetics in patients with hepatic impairment has not been investigated (see section 4.2).

Pharmacokinetics in children
In children zalcitabine plasma concentration is lower and the half-life is shorter than in adults given comparable doses, suggesting that zalcitabine may be cleared more rapidly in children than in adults (see section 4.4).

5.3 Preclinical safety data

Experimental animals are species-specifically rather insensitive to the toxicological potential of zalcitabine: the lowest plasmatic adverse effect levels of zalcitabine are 462 times the human exposure in rats, respectively 1825 times in dogs and 21 times in cynomolgus monkeys.

Carcinogenesis
High doses of zalcitabine, administered perorally to mice over 3 months up to two years induced increased incidences of thymic lymphomas in the female animals. Although the pathogenesis of the effect is uncertain, a predisposition to chemically induced thymic lymphoma has previously been noted in mice. Lymphoma has been identified as a consequence of HIV infection in humans. This most likely represents a consequence of prolonged immunosuppression and not antiviral therapy.

Mutagenesis
Zalcitabine was not mutagenic in vitro in bacterial and mammalian test systems (AMES test, mouse lymphoma Tk assay, HGPRT assay in V79 cells, UDS test in rat hepatocytes), but clastogenic in vitro in human lymphocytes and in vivo in the mouse micronucleus assay.

Fertility
Fertility and reproductive performance were assessed in rats at plasma concentrations up to 2142 times those achieved with the maximum recommended human dose (MRHD) based on AUC measurements. No adverse effects on rate of conception or general reproductive performance were observed. Plasma concentrations equivalent to or greater than 485 times the MRHD were associated with embryotoxicity.

Embryotoxicity and teratogenicity
HIVID is teratogenic in the tested species (mouse, rat). A variety of structural malformations (limbs, craniofacial, brain) were induced under very high exposure conditions. In a rat whole embryo culture system the combination of zalcitabine with zidovudine resulted in severe growth retardation and morphological abnormalities not seen with either drug alone (see section 4.6).

Pre- and postnatal toxicity
In a rat study with treatment during late gestation and lactation, learning and memory were impaired. For these observations, a clear no-effect level has not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Microcrystalline cellulose
Croscarmellose sodium
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)
Magnesium stearate
Hypromellose
Macrogol
Polysorbate 80
Titanium dioxide (E171)
Black printing inks: (a) OPACODE black S-1R-8100HV (pharmaceutical glaze, synthetic black iron oxide, lecithin, simethicone) (b) OPACODE black A-10450 (pharmaceutical shellac, synthetic black iron oxide, polysorbate 20)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Glass bottles:	Do not store above 30°C.
Aluminium blister:	Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

a) Glass bottle with a tight screw closure fitted with a desiccant unit containing 90 or 100 film-coated tablets (amber glass type III). Not all pack sizes may be marketed.

b) Aluminium blisters with aluminium on both sides in pack sizes of 90 or 100 film-coated tablets. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
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Welwyn Garden City
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8 MARKETING AUTHORISATION NUMBER

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