The European Agency for the Evaluation of Medicinal Products

ANNEX I

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Invirase

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule of Invirase contains saquinavir mesylate corresponding to 200mg saquinavir.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Invirase in combination with antiretroviral nucleoside analogues is indicated for the treatment of HIV-1 infected adult patients. (See also section 4.4)

4.2 Posology and method of administration

Adults and children over the age of 16 years
The recommended regimen for combination therapy with nucleoside analogues is 600mg of Invirase three times daily within 2 hours after a meal. For the recommended dose of the nucleoside analogues in combination therapy, please refer to the complete prescribing information for these drugs. For information on special patient groups refer to section 4.4, “Special warnings and special precautions for use”.

Dose adjustments

Invirase in combination therapy: For toxicities that may be associated with Invirase the treatment with Invirase should be interrupted. Invirase at doses less than 600mg tid is not recommended.

Hepatic and/or renal impairment: For information on hepatic and renal impairment refer to section 4.4, “Special warnings and special precautions for use”.

4.3 Contra-indications

Invirase is contraindicated in patients with hypersensitivity to saquinavir or to any of the other components contained in the capsule.

Invirase is contraindicated in patients receiving terfenadine, astemizole or cisapride (see section 4.5).

Invirase is contraindicated in patients receiving concomitant administration of drugs which decrease plasma concentrations of saquinavir, e.g. rifampicin, rifabutin or nevirapine (see section 4.5).

4.4 Special warnings and special precautions for use

Patients should be informed that saquinavir is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should also be advised that they may experience toxicities associated

with co-administered medications such as zalcitabine and zidovudine.

In view of the limited and/or variable bioavailability of Invirase, the risk of undertreatment should be considered. Careful consideration should therefore be given to the full regimen of anti-HIV medication.

Hepatic impairment: In cases of mild to moderate impairment no initial dosage adjustment is necessary at the recommended dose. The use of saquinavir by patients with severe hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increases in saquinavir levels may occur.

In patients with prior hepatitis B or hepatitis C and/or chronic alcoholism there have been reports of worsening of liver disease and development of portal hypertension after starting saquinavir. Associated symptoms include jaundice, ascites, oedema and, in some cases, oesophageal varices. Several of these patients died. A causal relationship between saquinavir therapy and development of portal hypertension has not been established. Co-administration of saquinavir with drugs known to cause hepatotoxicity should be avoided in these patients.

Renal impairment: Renal clearance is only a minor elimination pathway, the principal route of metabolism and excretion for saquinavir being via the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied and caution should be exercised when prescribing saquinavir in this population.

Patients with chronic diarrhoea or malabsorption: No information on safety and efficacy of saquinavir is available for patients suffering from chronic diarrhoea or malabsorption. It is unknown whether patients with such conditions could receive subtherapeutic drug levels.

Young and elderly patients: The safety and efficacy of saquinavir in HIV-infected patients (younger than 16 years) have not been established. Only limited experience is available in patients older than 60 years.

Lactose intolerance: Each capsule contains lactose (anhydrous) 63.3 mg. This quantity is probably not sufficient to induce specific symptoms of intolerance.

Use during pregnancy and lactation: *refer to section 4.6*

Patients with haemophilia: There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with proteinase inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with proteinase inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding**.**

Diabetes mellitus and hyperglycaemia: New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving proteinase inhibitors. In some of these the hyperglycaemia was severe and in some cases was also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.

Interaction with ritonavir: Plasma concentrations of saquinavir increase if co-administered with ritonavir ***(see section 4.5)***. In some cases, co-administration of saquinavir and ritonavir has led to severe adverse reactions, mainly diabetic ketoacidosis. Therefore, combination therapy of saquinavir and ritonavir should be used with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of saquinavir with zalcitabine and/or zidovudine has been studied in adults. Absorption, distribution and elimination of each of the drugs are unchanged when they are used together.

Ranitidine: There was an increase in exposure when saquinavir was dosed in the presence of both ranitidine and food, relative to saquinavir dosed with food alone. This resulted in AUC values which were 67% higher. This increase is not thought to be clinically relevant and no dose adjustment of saquinavir is recommended.

Grapefruit juice: Co-administration of saquinavir and grapefruit juice as single administration in healthy volunteers results in a 50% and 100% increase in exposure to saquinavir for normal and double strength grapefruit juice, respectively. This increase is not thought to be clinically relevant and no dose adjustment of saquinavir is recommended.

Indinavir: Co-administration of indinavir (800 mg q8h) and single doses of saquinavir (600-1200 mg) resulted in an about fivefold increase in plasma saquinavir AUC. An increase of this magnitude is not expected to influence the safety profile of saquinavir. Hence, no dose adjustment of saquinavir or indinavir are recommended.

Nelfinavir: Co-administration of nelfinavir (750 mg tid x 4 days) with a single dose of 1200 mg saquinavir soft gelatine capsules resulted in an about fourfold increase in saquinavir AUC, while co-administration of multiple doses of saquinavir with single doses of nelfinavir resulted in only an 18 % increase in nelfinavir exposure. This increase in saquinavir exposure is not expected to influence the safety profile of Invirase. Hence, no dose adjustments of saquinavir or nelfinavir are recommended.

Nevirapine: Co-administration of nevirapine and saquinavir resulted in a 24% decrease in plasma saquinavir AUC and no change to nevirapine AUC.

Ritonavir: Ritonavir extensively inhibits the metabolism of saquinavir resulting in greatly increased saquinavir plasma concentrations. Compared to steady-state AUC and C_{max} values obtained from 114 patients that received saquinavir 600 mg tid, saquinavir exposures from patients treated with a combination regimen of saquinavir 400mg b.i.d and ritonavir 400 mg b.i.d increased at least 17-fold and 14-fold based on AUC and C_{max}, respectively. Saquinavir has not been shown to alter the pharmacokinetics of ritonavir following single or multiple oral doses in healthy volunteers. When used in combination therapy, doses greater than 400 mg bid of either ritonavir or saquinavir were associated with an increase in adverse reactions. (See also section 4.4).

Clarithromycin: Co-administration of clarithromycin (500 mg bid) with saquinavir soft gelatine capsules (1200 mg tid) resulted in a 1.8 fold increase in saquinavir plasma AUC, a 45 % increase in clarithromycin AUC and a 24 % decrease in clarithromycin 14-OH metabolite AUC. No dosage adjustments for either drug is required when the two drugs are co-administered at the dosed studied.

Inadvisable associations: Rifampicin (600mg once daily) was shown to decrease plasma

concentrations of saquinavir by 80%. Since this may result in sub-therapeutic concentrations of saquinavir, rifampicin should not be administered concomitantly with saquinavir. Rifabutin also reduces saquinavir plasma concentrations by 40%. Other drugs that induce CYP3A4 (e.g. phenobarbital, phenytoin, dexamethasone, carbamazepine) may also reduce saquinavir plasma concentrations. If therapy with such drugs is warranted, physicians should consider using alternatives when a patient is taking Invirase.

Co-administration of terfenadine and saquinavir leads to an increase in plasma terfenadine exposure (AUC) associated with a prolongation of QTc times. Hence, terfenadine is contraindicated in patients receiving saquinavir (see section 4.3).

Associations requiring precautions for use: Concomitant use of ketoconazole (200mg once daily) and saquinavir caused a 1.5-fold increase in plasma concentrations of saquinavir, with no increase in the elimination half-life or any change in the absorption rate. Ketoconazole pharmacokinetics are not affected by co-administration with saquinavir at a dose of 600mg three times daily. No dose adjustment for either drug is required when the two drugs are co-administered at the doses studied.

A similar increase in plasma concentration of saquinavir could occur with other compounds in this class, such as fluconazole, itraconazole and miconazole or with other inhibitors of the CYP3A4 isoenzyme.

Other potential interactions: Co-administration of astemizole or cisapride with drugs which are known to be potent inhibitors of the CYP3A pathway (i.e. ketoconazole, itraconazole, etc.) may lead to elevated plasma concentrations of astemizole or cisapride. Pharmacokinetic interaction studies with Invirase and astemizole or cisapride have not been conducted, and although saquinavir is not a strong inhibitor of CYP3A, physicians should use alternatives to astemizole or cisapride (see section 4.3). Other compounds that are substrates of CYP3A4 (e.g. calcium channel blockers, tacrolimus, dapsone, quinidine, triazolam, midazolam) may have elevated plasma concentrations when co-administered with saquinavir; therefore, patients should be monitored for toxicities associated with such drugs.

It is unknown, whether drugs which reduce the gastrointestinal transit time (e.g. metoclopramide and cisapride) could lead to lower saquinavir plasma concentrations.

4.6 Use during pregnancy and lactation

Pregnancy**:** Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or fetus, the course of gestation and peri- and postnatal development. Clinical experience in pregnant women is lacking. Until additional data become available, saquinavir should be given to pregnant women only after special consideration.

Lactation**:** There are no laboratory animal or human data available on secretion of saquinavir in breast milk. The potential for adverse reactions to saquinavir in nursing infants cannot be assessed and, therefore, breast-feeding should be discontinued prior to receiving saquinavir. Health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

It is not known whether saquinavir has an effect on the ability to drive and to use machines.

4.8 Undesirable effects

Saquinavir does not alter or add to the toxicity profile of zalcitabine and/or zidovudine, when given in combination.

For comprehensive dose adjustment recommendations and drug-associated adverse reactions for either zalcitabine or zidovudine or other drugs used in combination, physicians should refer to the complete product information for each of these drugs.

The most frequently reported adverse events among patients receiving Invirase (excluding those toxicities known to be associated with zidovudine and zalcitabine when used in combinations) were diarrhoea, abdominal discomfort and nausea.

The listing below is based on a pivotal study which included a treatment arm with saquinavir used as single drug (n=327). Adverse events (mild, moderate and severe) with an incidence >2% considered by the investigator at least remotely related to saquinavir are given.

Skin and appendages: rash (5%), pruritus (3%)

Central and peripheral nervous system: headache (8%), peripheral neuropathy (8%), numbness of extremities (6%), paraesthesia (5%), dizziness (2%)

Gastrointestinal system: diarrhoea (17%), nausea (8%), buccal mucosa ulceration (6%), abdominal discomfort (4%), vomiting (3%), abdominal pain (3%), flatulence (2%)

Body as a whole - general disorders: fatigue (4%), asthenia (2%), fever (2%)

Musculo-skeletal system disorders: pain (3%)

Other adverse effects
Serious adverse events at least possibly related to the use of saquinavir reported from clinical trials are listed below.

Confusion, ataxia and weakness; acute myeloblastic leukemia; haemolytic anaemia; attempted suicide; Stevens-Johnson syndrome; severe cutaneous reaction associated with increased liver function tests; thrombocytopenia and intracranial haemorrhage; exacerbation of chronic liver disease with Grade 4 elevated liver function test, jaundice, ascites; drug fever; bullous skin eruption and polyarthritis; nephrolithiasis; pancreatitis; intestinal obstruction; portal hypertension; and peripheral vasoconstriction.

These adverse events were reported from a database of >6000 patients; over 100 of whom had been on saquinavir therapy for >2 years. Patients received saquinavir either as monotherapy or in combination with a wide variety of other anti-retroviral drugs (nucleoside analogues, non-nucleoside reverse transcriptase inhibitors and proteinase inhibitors).

Serious and non-serious adverse events from post-marketing spontaneous reports, not mentioned above, for which a causal relationship to saquinavir cannot be excluded are listed below:
myalgia, somnolence, depression, seizures, anxiety, allergic reactions, hepatitis, diabetes mellitus and abnormal renal function.

Laboratory abnormalities

The most common marked laboratory abnormalities seen during treatment with saquinavir containing regimens were isolated CPK increase, glucose decrease, glucose increase, raised transaminase values and neutropenia.

4.9 Overdose

One patient exceeded the recommended daily dose of saquinavir (1800mg daily) by taking 8000mg at once. The patient was treated with induction of emesis within two hours after ingestion of the overdose. The patient did not experience any sequelae. In an exploratory small study, oral dosing with saquinavir at 3600mg per day has not shown increased toxicity through the first 16 weeks of treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antiviral agent, ATC code J05AE01

Mechanism of action: The HIV proteinase carries out specific cleavages of viral precursor proteins in infected cells, as an essential step in the creation of fully formed, infectious virus particles. These viral precursor proteins contain a type of cleavage site which is recognized only by HIV and closely

related viral proteinases. Saquinavir has been designed as a peptide-like structural mimetic of such cleavage sites. As a result, saquinavir fits closely into the HIV-1 and HIV-2 proteinase active sites, *in vitro* acting as a reversible and selective inhibitor, with approximately a 50,000-fold lower affinity for human proteinases.

Unlike nucleoside analogues (zidovudine, etc.), saquinavir acts directly on its viral target enzyme. It does not require metabolic activation. This extends its potential effectiveness into resting cells. Saquinavir is active at nanomolar concentrations in lymphoblastoid and monocytic lines and in primary cultures of lymphocytes and monocytes infected with laboratory strains or clinical isolates of HIV-1.

Experiments in cell culture show that saquinavir produces an additive to synergistic antiviral effect against HIV-1 in double and triple combination with various reverse transcriptase inhibitors (including zidovudine, zalcitabine, didanosine) without enhanced cytotoxicity.

Pharmacodynamic effects: The effects of saquinavir in combination with zalcitabine and zidovudine on biological markers (CD4 cell counts and plasma RNA) were evaluated in HIV-1 infected patients.

In a study (NV14256) with zidovudine pre-treated patients (CD4 $\geq 50 \leq 300$ cells/mm^3), the combination of saquinavir plus zalcitabine compared to zalcitabine monotherapy prolonged the time to first AIDS-defining illness or death.
The combination therapy reduced the risk of a patient having an AIDS-defining illness or dying by 53%. For death alone the combination therapy reduced the risk by 72%. This corresponds to a reduction in the rate of an AIDS-defining illness or death from 29.4% to 16.0% over 18 months. Similarly for death alone, the rate was reduced from 8.6% to 4.1% over 18 months. In the three treatment groups, median treatment duration was 11 to 13 months and median follow-up has been 17 months.
In this study the median CD4 cell count at baseline over all treatment arms was 156 to 176 cells/mm^3. The average change from baseline over 16 weeks (median DAVG16) for saquinavir plus zalcitabine was +26 cells/mm^3 for the CD4 cell count and -0.6 log10 RNA copies/ml of plasma for viral load. The peak mean increase in the CD4 cell count was 47 cells/mm^3 at week 16. The peak mean reduction in viral load was 0.7 log 10 RNA copies/ml of plasma at week 12.

Study SV14604 is a randomised, multi-centre, double blind phase III parallel study of zidovudine + zalcitabine, vs. saquinavir + zidovudine, vs. saquinavir + zidovudine + zalcitabine, in untreated/minimally treated HIV infected patients. A fourth treatment arm of zidovudine monotherapy was discontinued; patients originally on zidovudine monotherapy were switched to saquinavir + zidovudine + zalcitabine, constituting a "delayed" triple therapy group.

A total of 3485 patients were treated and had follow up data available (the intent to treat population). Median baseline CD4 across the 3 arms was 199-204 cells/ mm^3, and median baseline HIV RNA was 5.0-5.1 log_{10} copies/ml. Median duration of study drug treatment was approximately 14 months and the median duration of follow up for AIDS defining events and deaths approximately 17 months.

Progression to first AIDS defining event or death was significantly decreased for patients on saquinavir + zidovudine + zalcitabine with 76 first AIDS defining events/deaths compared to 142 events on zidovudine + zalcitabine (p=0.0001). An exploratory comparison of initial saquinavir + zidovudine + zalcitabine compared to the delayed triple therapy group showed superiority of initial triple therapy including saquinavir with 76 AIDS defining events or deaths on initial triple therapy vs. 116 on the initial zidovudine monotherapy-delayed triple therapy regimen (p=0.001).

Patients receiving triple therapy had greater increases in CD4 count, with a 71 cells/mm^3 median peak increase from baseline compared to a 40 cells/mm^3 median peak increase on zidovudine + zalcitabine. Similarly, reductions in HIV RNA were greater on triple therapy with a -1.5 log_{10} copies/ml median peak change from baseline compared to a -1.1 log10 copies/ml median peak change on zidovudine + zalcitabine. For both CD4 and HIV RNA, comparisons over 48 weeks between the triple therapy arm and zidovudine + zalcitabine reached statistical significance (p=0.0001).

Monotherapy is not recommended because antiviral activity has not been demonstrated.

Potential for resistance and cross-resistance to saquinavir:

Resistance: HIV isolates with reduced susceptibility to saquinavir have been selected after extensive *in vitro* passage using increasing concentrations of the compound. Analysis of the protease amino acid sequence in these isolates shows substitutions at positions 48 (glycine to valine = G48V) and 90 (leucine to methionine = L90M).
Changes to viral sensitivity to drug in culture (= "phenotypic resistance") or in protease amino acid sequence (= "genotypic resistance") have been investigated in clinical trials. Two particular viral protease mutations (L90M or G48V, the former predominating and the combination rare) are found in those saquinavir treated patients with resistant isolates. The overall incidence of genotypic resistance at about one year in a group of phase I/II patients treated in combination with nucleoside analogues (zalcitabine and/or zidovudine), was 38% (15 out of 39 patients). The clinical significance of phenotypic and genotypic changes associated with saquinavir therapy has not been established.

Cross-resistance to other antiretrovirals: Cross-resistance between saquinavir and reverse transcriptase inhibitors is unlikely because of their different enzyme targets. HIV isolates resistant to zidovudine are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to zidovudine.
To date, therapy with saquinavir has demonstrated a distinctive and consistent pattern of mutations. Investigations into cross-resistance are in progress.

5.2 Pharmacokinetic properties

Absorption and bioavailability in adults and effect of food: In healthy volunteers the extent of absorption (as reflected by AUC) after a 600mg oral dose of saquinavir was increased from 24ng.h/ml (CV 33%), under fasting conditions, to 161ng.h/ml (CV35%) when

saquinavir was given following a heavy breakfast (48g protein, 60g carbohydrate, 57g fat; 1006kcal).

The presence of food also increased the time taken to achieve maximum concentration from 2.4 hours to 3.8 hours and substantially increased the mean maximum plasma concentrations (C_{max}) from 3.0ng/ml to 35.5ng/ml. The effect of food has been shown to persist for up to 2 hours. Therefore, Invirase should be taken within 2 hours after a meal.
Absolute bioavailability averaged 4% (CV 73%, range: 1% to 9%) in 8 healthy volunteers who received a single 600 mg dose (3 x 200 mg) of saquinavir following a heavy breakfast. The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. Gastric pH has been shown to be only a minor component in the large increase in bioavailability seen when given with food.
After multiple oral doses (25 - 600mg tid) in the presence of food, the increase in exposure (50-fold) was greater than directly proportional to the increase in dose (24-fold). Following multiple dosing (600 mg tid) in HIV-infected patients (n=29), the steady state area under the plasma concentration versus time curve (AUC) was 2.5 times (95% CI 1.6 to 3.8) higher than that observed after a single dose.

HIV-infected patients administered saquinavir 600 mg tid, with the instructions to take saquinavir after a meal or substantial snack, had AUC and maximum plasma concentration (C_{max}) values which were about twice those observed in healthy volunteers receiving the same treatment regimen (see below).

Mean (%CV) AUC and C_{max} in patients and healthy volunteers

	AUC8 (dose interval) in ng·h/ml	C_{max} in ng/ml
Healthy volunteers (n=6)	359.0 (46)	90.39 (49)
Patients (n=113)	757.2 (84)	253.3 (99)

Distribution in adults: Saquinavir partitions extensively into the tissues. The mean steady-state volume of distribution following intravenous administration of a 12mg dose of saquinavir was 700L (CV 39%). Saquinavir shows a high degree of protein binding (approximately 98%) which is independent of concentration over the range 15-700ng/ml. In two patients receiving Invirase 600mg three times daily, cerebrospinal fluid concentrations of saquinavir were negligible when compared to concentrations from matching plasma samples.

Metabolism and elimination in adults*: In vitro* studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on *in vitro* studies, saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600mg 14C-saquinavir (n=8), 88% and 1% of the orally administered radioactivity, was recovered in faeces and urine, respectively, within 4 days of dosing. In an additional four subjects administered 10.5 mg 14C-saquinavir intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in faeces and urine, respectively, within 4 days of dosing. In mass balance studies, 13% of circulating saquinavir in plasma was present as unchanged drug after oral adminstration and the remainder present as metabolites. Following intravenous adminstration, 66% of circulating saquinavir is present as unchanged drug and the remainder as metabolites, suggesting that saquinavir undergoes extensive first pass metabolism.

Systemic clearance of saquinavir was high, 1.14 L/h/kg (CV 12%), slightly above the hepatic

plasma flow, and constant after intravenous doses of 6, 36 and 72 mg. The mean residence time of saquinavir was 7 hours (n=8).

5.3 Preclinical safety data

Acute and chronic toxicity: Oral acute and chronic toxicity and toxicokinetic studies in the mouse, rat, dog and marmoset have demonstrated good tolerance to saquinavir at high plasma exposure to the drug relative to that seen in man.

Mutagenesis: Studies, with and without metabolic activation (as appropriate) have shown that saquinavir has no mutagenic or genotoxic activity.

Carcinogenesis: Carcinogenicity studies of saquinavir are ongoing.

Reproductive toxicity: Refer to section 4.6, “Use during pregnancy and lactation”

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling: lactose (anhydrous), microcrystalline cellulose, povidone, sodium starch glycollate, talc, magnesium stearate.
Capsule shell: gelatine, iron oxide black, red and yellow (E172), indigocarmine (E132), titanium dioxide (E171).
Capsule appearance: light brown and green, opaque; marking “ROCHE” and the code “0245” on each half of the capsule shell.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Two years.

6.4 Special precautions for storage

Store in the closed original pack.

6.5 Nature and content of container

Container: amber glass bottles with plastic screw closure containing 270 capsules of Invirase.

6.6 Instructions for use, handling and disposal (if appropriate)

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, United Kingdom

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/96/026/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4/10/96

10. DATE OF REVISION OF TEXT

ANNEX II

ANNEX III
LABELLING AND PACKAGE LEAFLET

B. PACKAGE LEAFLET

Package Leaflet

INVIRASE (saquinavir) capsules 200mg

Name of the medicinal product

Invirase

If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

Composition
Invirase is available as capsules for oral use in an amber glass bottle containing 270 capsules. The active ingredient is saquinavir. One capsule of Invirase contains saquinavir mesylate corresponding to 200mg saquinavir. The capsules are light brown and green. Each half of the capsule shell is marked with the printing “ROCHE” and the code “0245”.

The capsule also contains the excipients (additional ingredients) lactose (anhydrous) 63.3mg, microcrystalline cellulose, povidone, sodium starch glycollate, talc and magnesium stearate.

The capsule shell consists of gelatine, iron oxide black, red and yellow (E172) indigocarmine, (E132), titanium dioxide (E171).

Type of medicine:
Invirase is an antiviral agent for the treatment of infection with the human immunodeficiency virus (HIV).

Marketing Authorization Holder
The Marketing Authorization holder is Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, United Kingdom.

Manufacturer:
The manufacturer is Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany.

When should Invirase be used?
Invirase is used by adult patients suffering from HIV infection. Invirase is prescribed for use in combination with nucleoside analogues.

When should Invirase *not* be used?
You must not take Invirase if you know that you are allergic to saquinavir or to any of the other ingredients.

Important information before taking Invirase
You should know that Invirase is not a cure for HIV infection and that you may continue to develop infections or other illnesses associated with HIV disease. You should therefore remain under the care of your doctor while taking Invirase.

Treatment with Invirase has not been shown to reduce the risk of transmission of HIV to others through sexual contacts or blood contamination.

There are certain conditions which you may have, or have had, which require special care before or while taking Invirase. Therefore, before using this medicine, you should have told your doctor if you suffer from diabetes mellitus, diarrhoea, liver or kidney disease or have allergies.

Pregnancy and breast-feeding
Inform your doctor if you are pregnant or planning to become pregnant. This medicine should be taken during pregnancy only after consultation with your doctor. Likewise, inform your doctor if you are breast feeding. Health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

Effects on ability to drive and use machines
It is not known whether Invirase has an effect on your ability to drive a car or operate machinery.

Interaction with other medicinal products and other forms of interaction
Before starting treatment, make sure your doctor knows if you are taking other medicines (including those not prescribed by your doctor). This is extremely important, as using more than one medicine at the same time can strengthen or weaken the effect of the medicines (e.g. indinavir, nelfinavir, nevirapine, ritonavir, rifampicin, rifabutin, phenobarbital, phenytoin, dexamethasone, carbamazepine, terfenadine, astemizole, cisapride, calcium channel blockers, clarithromycin, tacrolimus, dapsone, quinidine, triazolam, midazolam). Therefore you should not take Invirase with other drugs without your doctor's consent.

Special warnings
Never give this medicine to someone else, even if this person has the same disease or symptoms as you. Invirase may improve your condition, but you will remain infectious while taking it. Treatment with Invirase is not a cure for HIV infection. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

In addition, during your treatment, other infections linked to your weakened immunity (opportunistic infections), may arise. These will require specific, and sometimes preventive treatment. It is very important to consult your doctor regularly while taking Invirase.

You should contact your doctor if diarrhoea develops.

At present, there is insufficient information to recommend the use of Invirase in children under the age of 16 years and in adults over 60 years.

Each capsule contains lactose (anhydrous) 63.3mg. This quantity is probably not sufficient to induce specific symptoms of lactose intolerance.

How to take Invirase
Always take Invirase exactly as your doctor tells you to. The doctor will prescribe a suitable dose for you.

The treatment consists of three 200 mg capsules of Invirase, three times daily, within 2 hours after a meal. The total daily dose is 9 capsules of Invirase. The capsules should be swallowed unchewed together with water.

Duration of treatment
Continue to take this medicine until your doctor tells you otherwise.

Missing a dose
If you forget to take one dose, take this dose as soon as you remember together with some food. Then go on with the regular schedule as prescribed. Do not change the prescribed dose yourself.

Overdose
If you have taken more than the prescribed dose of Invirase, you must contact your doctor or pharmacist (chemist).

Undesirable effects
All medicines may cause some unwanted or side-effects. When treating HIV infection it is not always possible to differentiate between unwanted effects caused by Invirase or by any other medicines you take at the same time or by the complications of the infection. For these reasons it is very important to inform your doctor of any change in your condition.

The most frequently reported unwanted effects concern the gastrointestinal tract, with diarrhoea, abdominal discomfort and nausea being the most common.

Other unwanted, less frequently reported effects, which may occur are: rash, itching, headache, peripheral neuropathy (a disturbance of the nerves in the feet and hands that may take the form of numbness, pins and needles, shooting or burning pain), weakness, dizziness, depression, anxiety, seizures, sleepiness, mouth ulcers, abdominal pain, vomiting, fever, tiredness, muscular aches and pain, allergic reactions and hepatitis.

Your doctor will want to test your blood regularly to detect possible abnormalities such as anaemia, neutropenia, thrombocytopenia, elevation of liver enzyme levels, impairment of kidney function, changes in blood sugar levels. Cases of diabetes mellitus or increased blood sugar levels have been reported in patients receiving this treatment or another proteinase inhibitor.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another proteinase inhibitor. Should this happen to you, seek immediate advice from your doctor.

If you are concerned about these or any other unexpected effect(s), talk to your doctor or pharmacist (chemist).

How to store Invirase
Always keep this medicine in the closed original pack and out of sight and reach of children.

Do not use this medicine after the expiry date shown on the outer pack.

Remember to return any unused medicines to your pharmacist (chemist), who will arrange for environment-friendly disposal.

Date of last revision

Other information

For any information about this product, please contact the local representative of the Marketing Authorization Holder:

Belgique/België:
N.V. Roche S.A.
Rue Dantestraat 75,
1070 Bruxelles - Brussel
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