ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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 with advanced or progressive immunodeficiency.

Clinical benefits of the combination therapy with Invirase and zalcitabine on HIV infection in terms of disease progression and survival have been confirmed in a controlled study recruiting patients with previous prolonged zidovudine therapy. Clinical studies are underway to confirm the clinical benefit of saquinavir in combination with other antiretroviral agents. Refer also to section 5.1 “Pharmacodynamic properties”.

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.
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.

**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.

**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

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.

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.
**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.

**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 terfenadine, 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 terfenadine, astemizole or cisapride. Pharmacokinetic interaction studies with saquinavir and terfenadine, astemizole or cisapride have not been conducted, and although saquinavir is not a strong inhibitor of CYP3A, physicians should use alternatives to terfenadine, astemizole or cisapride. Other compounds that are substrates of CYP3A4 (e.g. calcium channel blockers, clindamycin, 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.

Plasma concentrations of saquinavir are expected to increase if co-administered with ritonavir. At this time, there is insufficient data available on efficacy and safety of this co-administration. As no recommendation on dose and schedule for either of the compounds can be made, these drugs should not be used concomitantly.

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, breastfeeding 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 listing below is based on the pivotal study which included a treatment arm with saquinavir used as single drug. 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 (4%)
Central and peripheral nervous system: headache (4%), peripheral neuropathy (4%)
Gastrointestinal system: diarrhoea (16%), abdominal discomfort (6%), buccal mucosa ulceration (6%), nausea (4%)
Body as a whole - general disorders: asthenia (4%)

Combination therapy: saquinavir and zalcitabine
Peripheral neuropathy is the major toxicity associated with zalcitabine administration. Saquinavir does not potentiate the development of peripheral neuropathy induced by zalcitabine.

Combination therapy: saquinavir with zalcitabine and zidovudine
There was no increase in the incidence of well-established zidovudine or zalcitabine related toxicities such as myositis, hematological abnormalities, pancreatitis, buccal mucosa ulceration or peripheral neuropathy when saquinavir was given in combination with both zidovudine and zalcitabine.

Other adverse effects
Single, rare cases of serious adverse effects considered possibly related to use of study drugs have been reported: Confusion, ataxia and weakness; acute myeloblastic leukemia; hemolytic anemia; attempted suicide; Stevens-Johnson syndrome; seizures; severe cutaneous reaction associated with increased liver function tests; thrombophlebitis; thrombocytopenia; exacerbation of chronic liver disease with Grade 4 elevated liver function test, jaundice, ascites; liver injury with icterus and elevated transaminases; drug fever; bullous skin eruption and polyarthritis; nephrolithiasis; pancreatitis leading to death.

Laboratory abnormalities
Combination therapy: saquinavir and zalcitabine
The most common marked laboratory abnormalities were isolated CPK increase, glucose decrease and raised transaminase values. The incidence of laboratory toxicity was similar for zalcitabine monotherapy and for the combination of saquinavir and zalcitabine.

Combination therapy: saquinavir and zidovudine
The most frequent marked laboratory abnormalities were isolated CPK increase, neutropenia and elevated transaminases.

Combination therapy: saquinavir with zalcitabine and zidovudine
The most frequent marked laboratory abnormalities were elevated CPK levels, decreased glucose levels, neutropenia and increased transaminase values. Laboratory abnormalities observed with the triple combination were similar to those of zalcitabine and zidovudine combination.
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 J05AX06

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 ≥ 50 ≤ 300 cells/mm3), 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/mm3. The average change from baseline over 16 weeks (median DAVG16) for saquinavir plus zalcitabine was +26 cells/mm3 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/mm3 at week 16. The peak mean reduction in viral load was 0.7 log10 RNA copies/mL of plasma at week 12.

In a study (V13330) with previously untreated patients (CD4 ≤ 300 cells/mm3), the combination with zidovudine reduced viral load and increased CD4 cell counts. The median CD4 cell count at baseline over all treatment arms was 157 to 249 cells/mm3. The average change from baseline over 16 weeks (median DAVG16) for saquinavir plus zidovudine in these anti-retroviral naive subjects was +52 cells/mm3 for the CD4 cell count and -1.1 log10 RNA copies/mL of plasma for viral load. The peak mean increase in the CD4 cell count was 79 cells/mm3 at week 16. The peak mean reduction in viral load was 1.6 log10 RNA copies/mL at week 16.
copies/mL of plasma at week 4. A confirmatory phase III study (SV14604) is ongoing in anti-retroviral naive patients (less than 4 months zidovudine-experienced).

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 ZDV are sensitive to saquinavir, and conversely, HIV isolates resistant to saquinavir are sensitive to ZDV.

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 (Cmax) 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 (Cmax) values which were about twice those observed in healthy volunteers receiving the same treatment regimen (see below).
Mean (%CV) AUC and Cmax in patients and healthy volunteers

<table>
<thead>
<tr>
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<th>AUC8 (dose interval) in ng·h/mL</th>
<th>Cmax in ng/mL</th>
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<tbody>
<tr>
<td>Healthy volunteers (n=6)</td>
<td>359.0 (46)</td>
<td>90.39 (49)</td>
</tr>
<tr>
<td>Patients (n=113)</td>
<td>757.2 (84)</td>
<td>253.3 (99)</td>
</tr>
</tbody>
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**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 administration and the remainder present as metabolites. Following intravenous administration, 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF TEXT
ANNEX II
HOLDER(S) OF THE MANUFACTURING AUTHORISATION(S) RESPONSIBLE FOR BATCH
RELEASE AND CONDITIONS OF THE MARKETING AUTHORISATION
A. HOLDER(S) OF THE MANUFACTURING AUTHORISATION(S)

Manufacturer responsible for importation and batch release of the finished medicinal product in the European Economic Area:

- Hoffmann-La Roche A.G., Emil-Barell-Strasse1, 79639 Genzach-Wyhlen, Germany.
  Manufacturing authorisation issued on 26 April 1996, by the Regierungspräsidium Freiburg, Germany.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to non-renewable restricted medical prescription

C. COMMITMENTS MADE BY THE MARKETING AUTHORISATION HOLDER

The applicant, after having been consulted agreed to submit to the EMEA, within the defined time-frame, the information requested by the CPMP (letter dated 19 June 1996).


1. Re-assessment

1. The final study report from NV 14256 (saquinavir/zalcitabine versus saquinavir versus zalcitabine) should be submitted to the CPMP at the latest by December 31st 1996. Changes in viral load in this study should be validated in terms of surrogacy for clinical benefits.

2. A study report from SV14604 (saquinavir/zidovudine/zalcitabine versus saquinavir/zidovudine versus zidovudine/zalcitabine) in antiretroviral naive patients (less than 4 months zidovudine-experienced) should be submitted at the latest by December 31st 1997. Interim results should be reported as soon as available.

2. Other obligations

1. The colouring matter (opacifier) titanium dioxide of the capsule shell should be tested and the method for identification should be provided at the latest by October 1st 1996.

2. Concerning the UV-dissolution rate method the standard deviation, relative standard deviation and confidence interval should be reported at the latest by October 1st 1996.

3. Further results of the on-going stability studies of the three full-scale production batches should be submitted at the latest by December 31st 1997, to confirm the stability of the drug product up to the proposed shelf life.

4. The applicant is recommended to investigate if the observation in question 25 (strong alteration in dissolution behaviour after storage of capsules at 30°C/75% RH and 40°C/25% RH) can be correlated to degradation. The results should be reported at the latest by October 1st 1996.
5. The final study reports of the carcinogenicity studies are awaited by June 30th 1998.

6. The applicant should further elucidate the major factors responsible for the low and variable bioavailability of saquinavir. Clinical data from studies elucidating the effect of reduced gastrointestinal transit time (either due to diarrhoea or malabsorption or due to concomitant treatment with drugs such as cholinergics) or altered gastric pH should be presented at the latest by December 31st 1997.

7. The Company is invited to present, preferably until June 30th 1997, a development plan for paediatric patients and agrees to inform the EMEA on the outcome of these investigations.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
Invirase  
saquinavir  
200 mg

270 capsules

For oral administration

Refer to the package leaflet before use

Each capsule contains saquinavir mesylate corresponding to 200 mg saquinavir. Also contains lactose (anhydrous) 63.3 mg, colourants (titanium dioxide E171, iron oxide E172, indigocarmine E132) and other constituents

The capsules should be swallowed whole

Medicine: keep out of reach of children

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

Marketing authorization number:

Batch number:

Expiry date:

Medicinal product subject to medical prescription
B. PACKAGE LEAFLET
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 other 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.

Complete information on the clinical effects of Invirase is not yet available, but further studies are in progress.

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 diarrhoea, liver or kidney disease or have allergies.
**regnancy 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. Some health experts recommend that HIV-infected women not breast feed their infants under any circumstances in order to avoid transmission of HIV.

**Invirase, driving and using 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. ritonavir, rifampicin, rifabutin, phenobarbital, phenytoin, dexamethasone, carbamazepine, terfenadine, astemizole, cisapride, calcium channel blockers, clindamycin, 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.

Invirase is prescribed by doctors in combination with other antiretroviral medicines such as zalcitabine or zidovudine. Invirase does not change or add to the well-known unwanted effects of these drugs. Inflammation and pain in your muscles, ulceration of the oral mucosa, pancreatitis and disturbances of the nerves in the feet and hands may develop in association with the use of zalcitabine or zidovudine in the combination. Disturbances of the nerves in the feet and hands may take the form of numbness, pins and needles, shooting or burning pain.

Your doctor will want to test your blood regularly to detect possible abnormalities such as anaemia, neutropenia, elevation of liver enzyme levels.

Other unwanted, less frequently reported effects, which may occur are: Rash, itching, weakness, dizziness, depression, reduced intellectual ability, irritability, frequent urination, constipation, abdominal pain, appetite disturbances.

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

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

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:
Rue Dantestraat 75,
1070 Bruxelles - Brussel
Tel: 02 525 82 11

Italia:
Piazza Durante 11,
20131 Milano
Tel: 02 2884

Luxembourg:
Refer to Belgique/België

Danmark:
Industriholmen 59,
2650 Hvidovre
Tel: 36 39 99 99

Nederland:
Postbus 42,
3640 AA Mijdrecht
Tel: 0297 291222

Deutschland:
Postfach 1270, 79630 Grenzach Wyhlen
Tel: 07624 140

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