ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Norvir oral solution 80 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Norvir oral solution contains 80mg of ritonavir per ml.

3. PHARMACEUTICAL FORM
Oral solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
Norvir is indicated in combination with antiretroviral nucleoside analogue(s) for the treatment of HIV-1 infected adult patients with advanced or progressive immunodeficiency.

Clinical endpoint data are only available in patients with advanced HIV-disease. In patients with less advanced HIV-disease only data based on biological markers such as viral load and CD4 cell count are yet available. In these patients studies on the effect of ritonavir on clinical endpoints are ongoing. See section 5.1 for the results of the important studies.

4.2. Posology and method of administration
Norvir solution is administered orally and should preferably be ingested with food. The recommended dosage of Norvir solution is 600 mg (7.5 ml) twice daily by mouth.

The bitter taste of Norvir solution may be lessened if mixed with chocolate milk.

Pediatric use: The safety and efficacy of ritonavir in children below the age of 12 have not been established.

Renal and hepatic impairment: Currently, there are no data specific to these patient populations and therefore specific dosage recommendations cannot be made. Ritonavir is principally metabolized and eliminated by the liver. Norvir should not be given to patients with severe hepatic insufficiency (see Section 4.3 contra-indications). Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

4.3 Contra-indications
Patients with known hypersensitivity to ritonavir or any of its excipients. Patients with severe hepatic insufficiency.

In vitro and in vivo studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. Based primarily on literature review, ritonavir is expected to produce large increases in the plasma concentrations of the following drugs: amiodarone, astemizole, bepridil, bupropion, cisapride, clozapine, encainide, flecainide, meperidine, pimozide, piroxicam, propafenone, propoxyphene, quinidine, and terfenadine.
These agents have recognized risks of arrhythmias, hematologic abnormalities, seizures, or other potentially serious adverse effects. These drugs should not be co-administered with ritonavir. Ritonavir in addition is likely to produce large increases in these highly metabolized sedatives and hypnotics: alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam and zolpidem. Due to the potential for extreme sedation and respiratory depression from these agents, they should not be co-administered with ritonavir.

Concomitant use of ritonavir and rifabutin is contraindicated because of clinical consequences such as uveitis resulting from a multifold increase of rifabutin serum concentrations.

4.4 Special warnings and special precautions for use

There are no data on the pharmacokinetics and safety of ritonavir in patients with significant hepatic or renal dysfunction. Ritonavir is principally metabolized and eliminated by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function (see Section 4.3 Contra-indications).

The safety and efficacy of ritonavir in children below the age of 12 have not been established. Therefore, ritonavir should be used in children below the age of 12 only when the potential benefits clearly outweigh the potential risks.

Human pharmacokinetic data for combination of Norvir with antiretroviral drugs other than zidovudine and didanosine (ddI) are not yet available. Although the clinical use of combinations with zalcitabine (ddC) and stavudine (d4T) in a relatively limited number of patients did not seem to be associated with unfavorable effects, the use of combinations of Norvir with other nucleoside analogues should be guided by cautious therapeutic and safety monitoring.

Extra monitoring is recommended when diarrhoea occurs. The relatively high frequency of diarrhoea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medications.

Preliminary animal and human data indicate that ritonavir, when given concomitantly with saquinavir, causes a large increase in saquinavir blood levels. Due to a lack of sufficient safety data, ritonavir should not be given concomitantly with saquinavir or other protease inhibitors.

Norvir oral solution contains 43 % ethanol, therefore concomitant administration of Norvir with disulfiram or drugs with disulfiram-like reactions (e.g. metronidazole) should be avoided.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease 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 medicaments and other forms of interaction

Refer also to CONTRA-INDICATIONS (Section 4.3)

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms with the following ranked order: CYP3A > CYP2D6 > CYP2C9. In addition to the drugs listed in the CONTRA-INDICATIONS section, the following drugs or drug classes are known or suspected to be metabolized by these same cytochrome P450 isozymes: immunosuppressants (e.g., cyclosporine, tacrolimus), macrolide antibiotics (e.g., erythromycin), various steroids (e.g., dexamethasone, prednisolone), other HIV-protease inhibitors, nonsedating antihistamines (e.g., loratidine), calcium channel antagonists, several tricyclic antidepressants (e.g., desipramine, imipramine, amitriptyline, nortriptyline), other antidepressants (e.g., fluoxetine, paroxetine, sertraline), neuroleptics (e.g., haloperidol, risperidone, thioridazine), antifungals (e.g., ketoconazole, itraconazole), morphinomimetics (e.g., methadone, fentanyl), carbamazepine,
warfarin, tolbutamide. Due to the potential for significant elevation of serum levels of these drugs they should not be used concomitantly with ritonavir without a careful assessment of the potential risks and benefits. Careful monitoring of therapeutic and adverse effects is recommended when these drugs are concomitantly administered with ritonavir.

There are no pharmacokinetic data available on the concomitant use of morphine with ritonavir. On the basis of the metabolism of morphine (glucuronidation) lower levels of morphine may be expected.

Norvir increases the AUCs (area under the curve) of the following drugs when administered concomitantly:

**Clarithromycin:** because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with renal impairment the following dosage adjustment should be considered: for creatinine clearance (CL\textsubscript{CR}) of 30 to 60 ml/min. the clarithromycin dose should be reduced by 50%, for CL\textsubscript{CR} < 30 ml/min. the clarithromycin dose should be reduced by 75%. Doses of clarithromycin > 1g/day should not be coadministered with Norvir.

**Desipramine:** dosage reduction of desipramine should be considered in patients taking the combination.

**Rifabutin and its active metabolite 25-O-desacetyl rifabutin:** concomitant use with ritonavir has resulted in a multifold increase in the AUC of rifabutin and its active metabolite 25-O-desacetyl rifabutin with clinical consequences. Therefore, the concomitant use of ritonavir and rifabutin is contraindicated. (see Section 4.3 Contra-indications).

Norvir decreases the AUCs of the following drugs when administered concomitantly:

**Zidovudine (AZT) and ddl:** zidovudine and ddl have little if any effect on ritonavir pharmacokinetics. Ritonavir decreased the mean zidovudine AUC by approx. 25% in a study which has not been of sufficient duration to reach steady state for ritonavir. Ritonavir resulted in a reduction of the mean ddl AUC by 13% when given 2.5 hours apart from ritonavir. Dose alteration of AZT or ddl during concomitant Norvir therapy should usually not be necessary. Human pharmacokinetic data for combination with antiretroviral drugs other than zidovudine and ddl are not yet available (see also 4.4 Special warnings and special precautions for use).

**Ethinyl estradiol:** because concomitant administration of ritonavir with a fixed combination oral contraceptive resulted in a reduction of the ethinyl estradiol mean AUC by 41%, increased doses of oral contraceptives containing ethinyl estradiol, or alternate methods of contraception should be considered.

**Theophylline:** an increased dosage of theophylline may be required, as concomitant use with ritonavir caused an approx. 45 % decrease in the AUC of theophylline.

**Fixed combination of sulfamethoxazole/trimethoprim:** the concomitant administration of Norvir and sulfamethoxazole/trimethoprim resulted in a 20 % reduction of the sulfamethoxazole AUC and a 20% increase of the trimethoprim AUC. Dose alteration of sulfamethoxazole/trimethoprim during concomitant Norvir therapy should not be necessary.

Because ritonavir is highly protein bound, the possibility of increased therapeutic and toxic effects due to protein binding displacement of concomitant medications should be considered.
4.6. Use during pregnancy and lactation

No treatment-related malformations were observed with ritonavir in either rats or rabbits. Developmental toxicity observed in rats (embryolethality, decreased fetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased fetal weights) occurred at a maternally toxic dosage. There are no studies in pregnant women. This drug should be used during pregnancy only if the potential benefits clearly outweigh the potential risks.

It is not known whether this drug is excreted in human milk. Milk excretion has not been measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species. HIV-infected women should not breast feed their infants under any circumstances to avoid transmission of HIV.

4.7. Effects on ability to drive and use machines

Norvir has not specifically been tested for its possible effects on the ability to drive a car or operate machines. As somnolence and dizziness are known undesirable effects, this should be taken into account when driving or using machinery.

Norvir oral solution contains 43% alcohol.

4.8 Undesirable effects

In clinical studies (Phase II/III), the following adverse events with possible, probable or unknown relationship to ritonavir have been reported in ≥ 2% of 1033 patients:

Gastrointestinal: Nausea (47.5%), diarrhea (44.9%), vomiting (23.6%), abdominal pain (11.6%), taste perversion (11.4%); frequently dyspepsia, anorexia, local throat irritation; occasionally flatulence, dry mouth, eructation, mouth ulcer.

Nervous system: circumoral paresthesia (26.6%), peripheral paresthesia (15.4%); frequently dizziness, paresthesia, hyperesthesia, somnolence; occasionally insomnia, anxiety.

Skin: Frequently rash; occasionally pruritus, sweating.

Respiratory system: occasionally pharyngitis, cough increased.

Cardiovascular: Frequently vasodilation.

Others: Asthenia (22.3%), headache (15.5%); occasionally fever, pain, hyperlipemia, myalgia, weight loss, decrease of free and total thyroxine (T4) values.

Nausea, diarrhea, vomiting, asthenia, taste perversion, circumoral and peripheral paresthesia, and vasodilatation have been observed most frequently and are felt to be clearly related to ritonavir.

Clinical chemistry:

High gamma-glutamyl transpeptidase (GGT) (12%); frequently high creatine phosphokinase (CPK), high triglycerides, high alanine transaminase (SGPT); occasionally high aspartate transaminase (SGOT), high amylase, high uric acid, low potassium, high glucose, low total calcium, high magnesium, high total bilirubin, high alkaline phosphatase.

Hypertriglyceridemia, hypercholesterolemia and hyperuricemia were clearly related to ritonavir therapy.

Hematology:
Low white blood cell (WBC) (16%); occasionally low hemoglobin, low neutrophils, high eosinophils, high WBC, high neutrophils, high prothrombin time.

4.9 Overdose

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days and reported paresthesia which resolved after the dose was decreased.

The signs of toxicity observed in animals (mice and rats) included decreased activity, ataxia, dyspnea and tremors.

There is no specific antidote for overdose with ritonavir. Treatment of overdose with ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Due to the solubility characteristics and possibility of transintestinal elimination, it is proposed that management of overdose could entail gastric lavage and administration of activated charcoal. Since ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic group: antiviral for systemic use. ATC code: JO5AX

Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor which leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.

*In vitro* data indicates that ritonavir is active against all strains of HIV tested in a variety of transformed and primary human cell lines. The concentration of drug that inhibits 50% and 90% of viral replication *in vitro* is approximately 0.02 µM and 0.11µM, respectively. Similar potencies were found with both AZT-sensitive and AZT-resistant strains of HIV. Studies which measured direct cell toxicity of ritonavir on several cell lines showed no direct toxicity at concentrations up to 25 µM, with a resulting *in vitro* therapeutic index of at least 1000.

Resistance

Ritonavir-resistant isolates of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to ritonavir and genotypic analysis showed that the resistance was attributable primarily to specific amino acid substitutions in the HIV-1 protease at codons 82 and 84.

Susceptibility of clinical isolates to ritonavir was monitored in controlled clinical trials. Some patients receiving ritonavir monotherapy developed HIV strains with decreased susceptibility to drug. Serial genotypic and phenotypic analysis indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at position 82 from wildtype valine to usually alanine or phenylalanine (V82A/F). Viral strains isolated *in vivo* without a change at codon 82 did not have decreased susceptibility to ritonavir.
Cross-resistance to other antiretrovirals
Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in vitro but did not demonstrate a concordant decrease in susceptibility to saquinavir in vitro when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decrease susceptibility to indinavir in vitro (8-fold). Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested in vitro retained full susceptibility to ritonavir.

Clinical pharmacodynamic data
The effects of ritonavir (alone or combined with other antiretroviral agents) on biological markers of disease activity such as CD4 cell count and viral RNA were evaluated in several studies involving HIV-1 infected patients. The following studies are the most important.

A controlled study with ritonavir as add-on therapy in HIV-1 infected patients extensively pre-treated with nucleoside analogues and baseline CD4 cell counts ≤ 100 cells/µl showed a reduction in mortality and AIDS defining events. The mean average change from baseline over 16 weeks for HIV RNA levels was -0.79 log₁₀ (maximum mean decrease:1.29 log₁₀ ) in the ritonavir group vs -0.01 log₁₀ in the control group. The most frequently used nucleosides in this study were zidovudine, stavudine, didanosine and zalcitabine.

In a study recruiting less advanced HIV-1 infected patients (CD4 200-500 cells/µl) without previous antiretroviral therapy, ritonavir in combination with zidovudine or alone reduced viral load in plasma and increased CD4 count. The effects of ritonavir monotherapy seemed unexpectedly to be at least as large as the combination therapy, a finding which has not been explained adequately. The mean average change from baseline over 16 weeks for HIV RNA levels was -1.03 log₁₀ in the ritonavir group vs -0.80 log₁₀ in the ritonavir+ zidovudine group vs -0.42 log₁₀ in the zidovudine group. Clinical endpoint results of this study are not yet available.

The use of ritonavir monotherapy can not be recommended because of concern about the emergence of resistance.

In an open label trial in 32 antiretroviral naive HIV-1 infected patients the combination of ritonavir with zidovudine and zalcitabine decreased the viral load (mean decrease at week 20 of -1.76 log₁₀ ).

Studies investigating optimal combinations and the long term efficacy and safety of ritonavir are ongoing.

5.2. Pharmacokinetic properties
There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV positive adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir were observed to decrease over time, possibly due to enzyme induction, but appeared to stabilize by the end of 2 weeks. At steady state with a 600 mg bid dose, maximal concentration (Cmax) and trough concentration (Ctrough) values of 11.2 ± 3.6 and 3.7 ± 2.6 µg/ml (mean ± SD) were observed, respectively. The half life (t₁/₂) of ritonavir was approximately 3 to 5 hours. The steady-state apparent clearance in patients treated with 600 mg bid has averaged 8.8 ± 3.2 L/h. Renal clearance averaged less than 0.1 L/h and was relatively constant throughout the dosage range. The time to maximum concentration (Tmax) remained constant at approximately 4 hours with increasing dose.

The pharmacokinetics of ritonavir are dose-dependent: more than proportional increases in the AUC and Cmax were reported with increasing dose. Ingestion with food results in higher ritonavir exposure than ingestion in the fasted state.
No clinically significant differences in AUC or $C_{\text{max}}$ were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass.

The apparent volume of distribution ($V_B/F$) of ritonavir is approximately 20-40 L after a single 600 mg dose. The protein binding of ritonavir in human plasma was noted to be approximately 98-99%. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities. Plasma protein binding is constant over the concentration range of 0.1-100 mg/ml.

Tissue distribution studies with $^{14}$C-labeled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of drug. Tissue to plasma ratios of approximately 1 measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Ritonavir was noted to be extensively metabolized by the hepatic cytochrome P450 system, primarily isozyme CYP3A4 and to a lesser extent CYP2D6. Animal studies as well as \textit{in vitro} experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent drug.

Human studies with radiolabeled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

5.3 Preclinical safety data

Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of drug-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of drug. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Long-term carcinogenicity studies of ritonavir in animal systems have not been completed. However, ritonavir was not found to be mutagenic or clastogenic in a battery of \textit{in vitro} and \textit{in vivo} assays including the Ames bacterial reverse mutation assay using \textit{S. typhimurium} and \textit{E. coli}, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norvir oral solution contains: ethanol, purified water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid, saccharin sodium, peppermint oil, creamy caramel flavour, and dye E110.

6.2 Incompatibilities

Norvir should not be diluted with water.
6.3 Shelf-life

24 months under recommended storage conditions.

6.4 Special precautions for storage

Norvir oral solution should be stored under refrigeration between 2º-8ºC until it is dispensed to the patient. Refrigeration by the patient is not required if used within 30 days and stored below 30ºC.

Avoid exposure to excessive heat.

6.5 Nature and contents of container

Norvir oral solution is supplied in amber coloured multiple-dose polyethylene terephthalate (PET) bottles in a 90 ml size. Each commercial pack contains 5 bottles of 90 ml (450ml). A dosage cup containing graduations at 3.75 ml (300 mg dose), 5 ml (400 mg dose), 6.25 ml (500 mg dose) and 7.5 ml (600mg dose) is provided.

6.6 Instructions for handling of dosing device

The dosage cup should be cleaned immediately with hot water and dish soap after use. When cleaned immediately, drug residue is removed. The device must be dry prior to use.

7. MARKETING AUTHORIZATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT
Norvir capsule 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Norvir capsule contains 100 mg ritonavir.

3. PHARMACEUTICAL FORM
Capsules.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
Norvir is indicated in combination with antiretroviral nucleoside analogue(s) for the treatment of HIV-1 infected adult patients with advanced or progressive immunodeficiency.

Clinical endpoint data are only available in patients with advanced HIV-disease. In patients with less advanced HIV-disease only data based on biological markers such as viral load and CD4 cell count are yet available. In these patients studies on the effect of ritonavir on clinical endpoints are ongoing. See section 5.1 for the results of the important studies.

4.2. Posology and method of administration
Norvir capsules are administered orally and should preferably be ingested with food. The recommended dosage of ritonavir capsules is 600 mg (6 capsules) twice daily by mouth.

Pediatric use: The safety and efficacy of ritonavir in children below the age of 12 have not been established.

Renal and hepatic impairment: Currently, there are no data specific to these patient populations and therefore specific dosage recommendations cannot be made. Ritonavir is principally metabolized and eliminated by the liver. Norvir should not be given to patients with severe hepatic insufficiency (see Section 4.3 contra-indications). Because ritonavir is highly protein bound it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

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Patients with known hypersensitivity to ritonavir or any of its excipients. Patients with severe hepatic insufficiency.

In vitro and in vivo studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformations. Based primarily on literature review, ritonavir is expected to produce large increases in the plasma concentrations of the following drugs: amiodarone, astemizole, bepridil, bupropion, cisapride, clozapine, encainide, flecaainide, meperidine, pimozide, piroxicam, propafenone, propoxyphene, quinidine, and terfenadine. These agents have recognized risks of arrhythmias, hematologic abnormalities, seizures, or other potentially serious adverse effects. These drugs should not be co-administered with ritonavir. Ritonavir in addition is likely to produce large increases in these highly metabolized sedatives and hypnotics: alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam and zolpidem. Due to the potential for extreme sedation and respiratory depression from these agents, they should not be co-administered with ritonavir.
Concomitant use of ritonavir and rifabutin is contraindicated because of clinical consequences such as uveitis resulting from a multifold increase of rifabutin serum concentrations.

4.4 Special warnings and special precautions for use

There are no data on the pharmacokinetics and safety of ritonavir in patients with significant hepatic or renal dysfunction. Ritonavir is principally metabolized and eliminated by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function (see Section 4.3 Contra-indications).

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Preliminary animal and human data indicate that ritonavir, when given concomitantly with saquinavir, causes a large increase in saquinavir blood levels. Due to a lack of sufficient safety data, ritonavir should not be given concomitantly with saquinavir or other protease inhibitors.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in haemophiliac patients type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than a half of the reported cases, treatment with protease 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.

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Norvir increases the AUCs (area under the curve) of the following drugs when administered concomitantly:

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**Desipramine**: dosage reduction of desipramine should be considered in patients taking the combination.

**Rifabutin and its active metabolite 25-O-desacetyl rifabutin**: concomitant use with ritonavir has resulted in a multifold increase in the AUC of rifabutin and its active metabolite 25-O-desacetyl rifabutin with clinical consequences. Therefore, the concomitant use of ritonavir and rifabutin is contraindicated. (see Section 4.3 Contra-indications).

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**Ethinyl estradiol**: because concomitant administration of ritonavir with a fixed combination oral contraceptive resulted in a reduction of the ethinyl estradiol mean AUC by 41%, increased doses of oral contraceptives containing ethinyl estradiol, or alternate methods of contraception should be considered.

**Theophylline**: an increased dosage of theophylline may be required, as concomitant use with ritonavir caused an approx. 45 % decrease in the AUC of theophylline.

**Fixed combination of sulfamethoxazole/trimethoprim**: the concomitant administration of Norvir and sulfamethoxazole/trimethoprim resulted in a 20 % reduction of the sulfamethoxazole AUC and a 20% increase of the trimethoprim AUC. Dose alteration of sulfamethoxazole/trimethoprim during concomitant Norvir therapy should not be necessary.

Because ritonavir is highly protein bound, the possibility of increased therapeutic and toxic effects due to protein binding displacement of concomitant medications should be considered.

### 4.6. Use during pregnancy and lactation

No treatment-related malformations were observed with ritonavir in either rats or rabbits. Developmental toxicity observed in rats (embryolethality, decreased fetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dosage. Developmental toxicity in rabbits (embryolethality, decreased litter size and decreased fetal weights) occurred at a maternally toxic dosage. There are no studies in pregnant women. This drug should be used during pregnancy only if the potential benefits clearly outweigh the potential risks.

It is not known whether this drug is excreted in human milk. Milk excretion has not been measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species. HIV-infected women should not breast feed their infants under any circumstances to avoid transmission of HIV.

### 4.7. Effects on ability to drive and use machines
Norvir has not specifically been tested for its possible effects on the ability to drive a car or operate machines. As somnolence and dizziness are known undesirable effects, this should be taken into account when driving or using machinery.

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In clinical studies (Phase II/III), the following adverse events with possible, probable or unknown relationship to ritonavir have been reported in > 2% of 1033 patients:

**Gastrointestinal**: Nausea (47.5%), diarrhea (44.9%), vomiting (23.6%), abdominal pain (11.6%), taste perversion (11.4%); frequently dyspepsia, anorexia, local throat irritation; occasionally flatulence, dry mouth, eructation, mouth ulcer.

**Nervous system**: circumoral paresthesia (26.6%), peripheral paresthesia (15.4%); frequently dizziness, paresthesia, hyperesthesia, somnolence; occasionally insomnia, anxiety.

**Skin**: Frequently rash; occasionally pruritus, sweating.

**Respiratory system**: occasionally pharyngitis, cough increased.

**Cardiovascular**: Frequently vasodilation.

**Others**: Asthenia (22.3%), headache (15.5%); occasionally fever, pain, hyperlipemia, myalgia, weight loss, decrease of free and total thyroxine ($T_4$) values.

Nausea, diarrhea, vomiting, asthenia, taste perversion, circumoral and peripheral paresthesia, and vasodilation have been observed most frequently and are felt to be clearly related to ritonavir.

**Clinical chemistry**:

High gamma-glutamyl transpeptidase (GGT) (12%); frequently high creatine phosphokinase (CPK), high triglycerides, high alanine transaminase (SGPT); occasionally high aspartate transaminase (SGOT), high amylase, high uric acid, low potassium, high glucose, low total calcium, high magnesium, high total bilirubin, high alkaline phosphatase.

Hypertriglyceridemia, hypercholesterolemia and hyperuricemia were clearly related to ritonavir therapy.

**Hematology**:

Low white blood cell (WBC) (16%); occasionally low hemoglobin, low neutrophils, high eosinophils, high WBC, high neutrophils, high prothrombin time.

4.9 Overdose

Human experience of acute overdose with ritonavir is limited. One patient in clinical trials took ritonavir 1500 mg/day for two days and reported paresthesia which resolved after the dose was decreased.

The signs of toxicity observed in animals (mice and rats) included decreased activity, ataxia, dyspnea and tremors.

There is no specific antidote for overdose with ritonavir. Treatment of overdose with ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Due to the solubility characteristics and possibility of transintestinal elimination, it is proposed that management of overdose could entail gastric lavage and administration of activated charcoal. Since ritonavir is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.
5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic group:  antiviral for systemic use. ATC code: JO5A X

Ritonavir is an orally active peptidomimetic inhibitor of the HIV-1 and HIV-2 aspartyl proteases. Inhibition of HIV protease renders the enzyme incapable of processing the gag-pol polyprotein precursor which leads to the production of HIV particles with immature morphology that are unable to initiate new rounds of infection. Ritonavir has selective affinity for the HIV protease and has little inhibitory activity against human aspartyl proteases.

In vitro data indicates that ritonavir is active against all strains of HIV tested in a variety of transformed and primary human cell lines. The concentration of drug that inhibits 50% and 90% of viral replication in vitro is approximately 0.02 µM and 0.11µM, respectively. Similar potencies were found with both AZT-sensitive and AZT-resistant strains of HIV. Studies which measured direct cell toxicity of ritonavir on several cell lines showed no direct toxicity at concentrations up to 25 µM, with a resulting in vitro therapeutic index of at least 1000.

Resistance
Ritonavir-resistant isolates of HIV-1 have been selected in vitro. The resistant isolates showed reduced susceptibility to ritonavir and genotypic analysis showed that the resistance was attributable primarily to specific amino acid substitutions in the HIV-1 protease at codons 82 and 84.

Susceptibility of clinical isolates to ritonavir was monitored in controlled clinical trials. Some patients receiving ritonavir monotherapy developed HIV strains with decreased susceptibility to drug. Serial genotypic and phenotypic analysis indicated that susceptibility to ritonavir declined in an ordered and stepwise fashion. Initial mutations occurred at position 82 from wildtype valine to usually alanine or phenylalanine (V82A/F). Viral strains isolated in vivo without a change at codon 82 did not have decreased susceptibility to ritonavir.

Cross-resistance to other antiretrovirals
Serial HIV isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in vitro but did not demonstrate a concordant decrease in susceptibility to saquinavir in vitro when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decrease susceptibility to indinavir in vitro (8-fold). Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested in vitro retained full susceptibility to ritonavir.

Clinical pharmacodynamic data
The effects of ritonavir (alone or combined with other antiretroviral agents) on biological markers of disease activity such as CD4 cell count and viral RNA were evaluated in several studies involving HIV-1 infected patients. The following studies are the most important.

A controlled study with ritonavir as add-on therapy in HIV-1 infected patients extensively pre-treated with nucleoside analogues and baseline CD4 cell counts ≤ 100 cells/µl showed a reduction in mortality and AIDS defining events. The mean average change from baseline over 16 weeks for HIV RNA levels was -0.79 log₁₀ (maximum mean decrease:1.29 log₁₀ ) in the ritonavir group vs -0.01 log₁₀ in the control group. The most frequently used nucleosides in this study were zidovudine, stavudine, didanosine and zalcitabine.

In a study recruiting less advanced HIV-1 infected patients (CD4 200-500 cells/µl) without previous antiretroviral therapy, ritonavir in combination with zidovudine or alone reduced viral load in plasma and increased CD4 count. The effects of ritonavir monotherapy seemed unexpectedly to be at least as large as the combination therapy, a finding which has not been explained adequately. The mean average change from baseline over 16 weeks for HIV RNA levels was -1.03 log₁₀ in the ritonavir group vs -0.80 log₁₀ in
the ritonavir + zidovudine group vs -0.42 log₁₀ in the zidovudine group. Clinical endpoint results of this study are not yet available.

The use of ritonavir monotherapy can not be recommended because of concern about the emergence of resistance.

In an open label trial in 32 antiretroviral naive HIV-1 infected patients the combination of ritonavir with zidovudine and zalcitabine decreased the viral load (mean decrease at week 20 of -1.76 log₁₀).

Studies investigating optimal combinations and long term efficacy and safety of ritonavir are ongoing.

5.2. Pharmacokinetic properties

There is no parenteral formulation of ritonavir, therefore the extent of absorption and absolute bioavailability have not been determined. The pharmacokinetics of ritonavir during multiple dose regimens were studied in non-fasting HIV positive adult volunteers. Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir were observed to decrease over time, possibly due to enzyme induction, but appeared to stabilize by the end of 2 weeks. At steady state with a 600 mg bid dose, maximal concentration (C max ) and trough concentration (C trough ) values of 11.2 ± 3.6 and 3.7 ± 2.6 µg/ml (mean ± SD) were observed, respectively. The half life (t₁/₂) of ritonavir was approximately 3 to 5 hours. The steady-state apparent clearance in patients treated with 600 mg bid has averaged 8.8 ± 3.2 L/h. Renal clearance averaged less than 0.1 L/h and was relatively constant throughout the dosage range. The time to maximum concentration (T max ) remained constant at approximately 4 hours with increasing dose.

The pharmacokinetics of ritonavir are dose-dependent: more than proportional increases in the AUC and C max were reported with increasing dose. Ingestion with food results in higher ritonavir exposure than ingestion in the fasted state.

No clinically significant differences in AUC or C max were noted between males and females. Ritonavir pharmacokinetic parameters were not statistically significantly associated with body weight or lean body mass.

The apparent volume of distribution (V B/F) of ritonavir is approximately 20-40 L after a single 600 mg dose. The protein binding of ritonavir in human plasma was noted to be approximately 98 - 99%. Ritonavir binds to both human alpha 1-acid glycoprotein (AAG) and human serum albumin (HSA) with comparable affinities. Plasma protein binding is constant over the concentration range of 0.1-100 mg /ml.

Tissue distribution studies with ¹⁴C-labeled ritonavir in rats showed the liver, adrenals, pancreas, kidneys and thyroid to have the highest concentrations of drug. Tissue to plasma ratios of approximately 1 measured in rat lymph nodes suggests that ritonavir distributes into lymphatic tissues. Ritonavir penetrates minimally into the brain.

Ritonavir was noted to be extensively metabolized by the hepatic cytochrome P450 system, primarily isozyme CYP3A4 and to a lesser extent CYP2D6. Animal studies as well as in vitro experiments with human hepatic microsomes indicated that ritonavir primarily underwent oxidative metabolism. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug. However, the AUC of the M-2 metabolite was approximately 3% of the AUC of parent drug.

Human studies with radiolabeled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir. In these studies renal elimination was not found to be a major route of elimination of ritonavir. This was consistent with the observations in animal studies.

5.3 Preclinical safety data
Repeated dose toxicity studies in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium (RPE) and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of drug-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of drug. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests. Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Long-term carcinogenicity studies of ritonavir in animal systems have not been completed. However, ritonavir was not found to be mutagenic or clastogenic in a battery of in vitro and in vivo assays including the Ames bacterial reverse mutation assay using S. typhimurium and E. coli, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norvir gelatine capsules contain: saturated polyglycolyzed glycerides, ethanol, polyoxyl 35 castor oil, propylene glycol, medium chain triglycerides, polysorbate 80, and anhydrous citric acid. The banding components are: gelatine and polysorbate 80. The printing ingredients are: shellac, blue 2 and titanium dioxide.

6.2 Incompatibilities

None known.

6.3 Shelf-life

12 months under recommended storage conditions.

6.4 Special precautions for storage

Norvir capsules should be stored under refrigeration between 2º-8ºC at all times.

Avoid exposure to freezing and excessive heat.
6.5 Nature and contents of container

Norvir capsules are supplied in amber coloured high density polyethylene (HDPE) bottles containing 84 capsules. Each commercial pack contains 4 bottles of 84 capsules (336 capsules).

7. MARKETING AUTHORIZATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

MANUFACTURING AUTHORISATIONS AND CONDITIONS OF THE MARKETING AUTHORISATION
A. HOLDER OF THE MANUFACTURING AUTHORISATION

Manufacturers of the active substance:

- Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064-4000, USA
- Ajinomoto, 1730 Hinago-cho Yokkaichi, Mie Prefecture 510, Japan.
- Finorga, Route de Givors, 38670 Chasse-sur-Rhone, France.
- Archimica, S.p.A., Vaile Europa 5, 21040 Origgio (Varese), Italy.
- Abbott Laboratories Limited, Queenborough, Kent ME11 5EL, United Kingdom
- Abbott S.p.A., 104010 Campoverde di Aprilia (Latina), Italy.

Manufacturer of the finished medicinal product for the capsule:

- Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064-4000, USA.

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


Manufacturer of the finished medicinal product for the oral solution and site where the batch release takes place:


B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to non-renewable restricted medical prescription.
C. SPECIFIC OBLIGATIONS OF 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 22 May 1996).

Commitments on clinical aspects presented in paragraph 1 shall form the basis of a re-assessment of the benefit/risk profile of the medicinal product pursuant to Part 4G of Council Directive 75/318/EEC.

1. Re-assessment

1. Not later than September 1, 1996, the finalised study report of protocol M94-247 and not later than March 1, 1997, that of protocol M94-245 will be submitted by the applicant to the EMEA.

The paradoxical result of protocol M94-245 will be reanalysed and explained in detail on the basis of long term biological marker and clinical endpoint data of the requested final study report.

A “worst case scenario analysis” (patients lost to follow up, dropouts, and deaths during first month on study) will be provided by the applicant with the requested final study report of protocol M94-247. The analysis of the predictive value of biological marker changes (viral load, CD4 count) for AIDS defining events or death will be included in this final study report.

Long term ocular and immunological safety results of the pivotal trials will be provided with the final study reports. In addition, monitoring of ocular and immunological safety will be included in all protocols of planned major clinical studies.

2. Not later than September 1, 1996, the applicant will submit to the EMEA a detailed study program for an expanded investigation of antiretroviral combination therapy that will include long term efficacy and safety data. In addition, the emergence of HIV resistant strains to ritonavir will be investigated and characterised.

2. Other obligations

a. Chemical, pharmaceutical and biological aspects

When results of the long term stability studies are available, the limits (single and total) of the different degradation products will be reassessed (September 30, 1998).

Oral solution

1. The applicant will comment on the kind of rework procedures by July 31, 1996.

2. The chemical name of ritonavir will be clarified and it will be shown that it is conforming with international conventions, or it has to be revised accordingly by July 31, 1996.

3. Batch analysis will be provided from the manufacturing sites Abbott UK and Abbott Italy, with results of the final synthetic process, by December 31, 1996.

4. A certificate of analysis for all excipients used will be provided by July 31, 1996.
5. A description of the general qualitative composition mentioning the main constituents of Flavor Creamy Caramel (WL-23,669) with an appropriate process of identification will be given by July 31, 1996.

6. Additional stability data will be submitted by July 31, 1996.

7. Stability data on production batches will be presented on an ongoing basis, at least every 6 months.

Capsules

1. An assay in the release and shelf-life specification will be considered if there is also an impact of excipients such as polysorbate 80, medium chain triglycerides and saturated polyglycolised glycerides on bioavailability by July 31, 1996.

2. A certificate of analysis for all excipients used will be provided by July 31, 1996.

3. The qualitative and quantitative composition of the components of the capsule shell will be given by July 31, 1996.

4. Saturated polyglycolised glycerides: a monograph detailing the quality characteristics of the chosen material Gelucire 50/13 ( specifications and control methods) will be presented by July 31, 1996.

5. The discriminatory power of the dissolution test is to be discussed, in combination with the large scatter in the results of this parameter found in the batch analysis by July 31, 1996.

6. A comment on the very different results concerning the dissolution testing of the various capsule batches, especially a comment on batch 08-216-AR-03 which does not comply with the specification (> 75% released after 90 minutes) will be made by July 31, 1996.

7. A “key” for cross reference for attachment 3 to format 18 of the Expert Report tabulates will be provided by July 31, 1996.

8. Additional stability data will be submitted by July 31, 1996.

9. Stability data on production batches will be presented on an ongoing basis, at least every 6 months.

b. Toxicological and pharmacological aspects

1. The interspecies comparison of exposure must be reviewed in the light of the observed species-dependent differences in plasma protein binding. $C_{\text{max}}$ and AUC values in the animal species used in toxicity testing have to be corrected for the percentage unbound and compared to those attained in ritonavir-treated patients. These reports will be submitted by December 1, 1996.

2. The full study report of the 12-month dog toxicity study will be submitted by October 1, 1996.

3. The full study reports of the carcinogenicity studies will be submitted by December 1, 1998.

c. Clinical aspects

The clinical trial programme will include well-controlled studies pertaining to the defined objectives.

1. The applicant will submit to the EMEA a complete phase I to III pediatric clinical trial programme by December 1, 1996.
2. The applicant will submit a study comparing the pharmacokinetics of ritonavir in patients with mild to moderate hepatic impairment with patients with normal hepatic function in order to obtain data which will allow more precise dosing recommendations for this group of patients by June 1, 1997.

3. The applicant will submit to the EMEA special, targeted interaction trials (cross-over trials covering the steady state period of ritonavir) for drugs used often concomitantly in HIV infected patients (e.g. ketoconazole, itraconazole, morphinomimetics and benzodiazepines) or used to reduce side effects of ritonavir treatment by June 1, 1997.

4. The result of a cross-over bioequivalence trial comparing the marketed semisolid capsules (formulation L) and aqueous solution (formulation K5) will be submitted to the EMEA by June 1, 1997.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. - LABELLING
Norvir™
Ritonavir Oral Solution 80 mg/ml
Contains: 450 ml (5 bottles of 90 ml each)
Each 7.5 ml (marked dosing cup enclosed) contains ritonavir 600 mg.

contains alcohol (43% by volume), polyoxyl 35 castor oil, propylene glycol, saccharin sodium.

oral route

See enclosure for prescribing information.

Store in refrigerator between 2º-8ºC until dispensed to the patient. Refrigeration by the patient is not required if used within 30 days and stored below 30ºC. Avoid exposure to excessive heat. Keep tightly closed.

Medicinal product subject to medical prescription
Keep out of reach of children.

Child resistant closure.

Batch no:
Expiry date:
Marketing authorization no.:

Marketing authorization holder: Abbott Laboratories Limited
Queenborough
Kent ME11 5EL United Kingdom
NORVIR™ ORAL SOLUTION LABEL TEXT

Norvir
Ritonavir Oral Solution 80 mg/ml
90 ml
Each 7.5 ml (marked dosing cup enclosed) contains ritonavir 600 mg.

contains alcohol (43% by volume), polyoxyl 35 castor oil, propylene glycol, saccharin sodium.

oral route

See enclosure for prescribing information.

Store in refrigerator between 2º-8ºC until dispensed to the patient.
Refrigeration by the patient is not required if used within 30 days and stored below 30ºC.
Avoid exposure to excessive heat. Keep tightly closed.

Medicinal product subject to medical prescription
Keep out of reach of children.

Child resistant closure.

Batch no:
Expiry date:
Marketing authorization no.:

Marketing authorization holder: Abbott Laboratories Limited
Queenborough
Kent ME11 5EL United Kingdom
NORVIR CAPSULES CARTON TEXT

Norvir™
Ritonavir capsules 100 mg
Contains: 336 capsules (4 bottles of 84 capsules each)
Each capsule contains 100 mg ritonavir

contains polyoxyl 35 castor oil, propylene glycol
oral route

See enclosure for prescribing information

Store in refrigerator between 2º-8ºC
Avoid exposure to excessive heat.

Medicinal product subject to medical prescription.
Keep out of reach of children.

Child resistant closure.

Batch no:
Expiry date:
Marketing authorization no.:

Marketing authorization holder: Abbott Laboratories Limited
Queenborough
Kent ME11 5EL United Kingdom
Norvir™
Ritonavir capsules 100 mg
Contains: 84 capsules
Each capsule contains 100 mg ritonavir

contains polyoxyl 35 castor oil, propylene glycol

oral route

See enclosure for prescribing information

Store in refrigerator between 2º-8ºC
Avoid exposure to excessive heat.

Medicinal product subject to medical prescription.
Keep out of reach of children.

Child resistant closure.

Batch no:
Expiry date:
Marketing authorization no.:

Marketing authorization holder: Abbott Laboratories Limited
Queenborough
Kent ME11 5EL United Kingdom
B. PACKAGE LEAFLET
Package Leaflet

NORVIR (ritonavir) oral solution 80 mg/ml

What Medication has been prescribed? (Name of the Medicinal Product and Composition)
NORVIR (ritonavir) oral solution contains 80 mg/ml of ritonavir dissolved in alcohol, water, polyoxyl 35 castor oil and propylene glycol. Other ingredients include saccharin sodium, anhydrous citric acid, peppermint oil, caramel flavoring and dye E110.

How is NORVIR supplied? (Pharmaceutical Forms)
NORVIR oral solution comes in a multiple-dose 90 ml amber bottle. 5 bottles of 90 ml are provided in one package. Each ml of Norvir contains 80 mg of ritonavir.
NORVIR is also supplied as a capsule containing 100 mg of ritonavir.

What is NORVIR? (Pharmaco-Therapeutic Group)
NORVIR is an inhibitor of the human immunodeficiency virus (HIV) protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to infect new cells.

Who should I call if I have questions about NORVIR?
If you have questions about NORVIR, ask your doctor or pharmacist or contact the local representative as listed at the end of this leaflet. Discuss all questions about your health with your doctor.

Why is NORVIR being prescribed for me? (Therapeutic Indications)
Your doctor has prescribed NORVIR to help control your HIV infection. NORVIR does this by slowing the spread of infection in your body.
Complete information on the clinical effects of Norvir is not yet available but further studies are in progress.
NORVIR can be given with certain other anti-HIV medicines. There is limited information on the use of Norvir with other drugs. Your doctor will determine which medicines are best for you.

Is there anyone who shouldn't take NORVIR? (Contra-indications)
People who are allergic to NORVIR or any of its ingredients should not take NORVIR.
Pregnant or nursing mothers should not take NORVIR unless specifically directed by their doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are nursing a baby. Health experts recommend that HIV-infected women should not breast feed their infants to avoid transmission of HIV.
Children younger than 12 years of age should not take NORVIR unless specifically directed by their doctor.

People with severe liver disease should not take NORVIR.
While taking NORVIR you must not take astemizole or terfenadine which are medicines commonly used to treat allergy symptoms and may be available without a prescription. While taking NORVIR you must not take alprazolam, amiodarone, bepridil, bupropion, cисаприл, clozapine, diazepam, encaïnide, estazolam, flecainide, flurazepam, meperidine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, rifabutin, triazolam or zolpidem. If you're currently taking any of these medicines, ask your doctor about switching to a different medicine while you're taking NORVIR. Often, there are other drugs you can take instead.
Norrir may interact with certain other medications with potential clinical consequences. The use of the following drugs together with Norvir should only take place on the basis of medical advice: immunosuppressants (e.g., cyclosporine, tacrolimus), macrolide antibiotics (e.g., erythromycin, clarithromycin), various steroids (e.g., dexamethasone, prednisolone, ethinyl estradiol), other HIV-protease inhibitors, nonseating antihistamines (e.g., loratidine), calcium channel antagonists, several tricyclic antidepressants (e.g., desipramine, imipramine, amitriptyline, nortriptyline), other antidepressants (e.g., fluoxetine, paroxetine, sertraline), neuroleptics (e.g., haloperidol, risperidone,
thioridazine), antifungals (e.g., ketoconazole, itraconazole), morphinomimetics (e.g., methadone, fentanyl), carbamazepine, warfarin, tolbutamide, theophylline. Be sure to tell your doctor about all of the medicines you're taking, even those that do not require a prescription.

WHAT ELSE SHOULD I KNOW ABOUT NORVIR? (Special Precautions for Use)
Even if you feel better, do not stop taking NORVIR without talking to your doctor. NORVIR has not been shown to lower the risk of passing HIV to others through sexual contact or blood transfer. You should use appropriate precautions. People with liver disease who take NORVIR may need additional testing. Your doctor will decide if this is needed for you. Using NORVIR as recommended should give you the best chance to delay the development of drug resistance. You should not take any OTC (over the counter) medicine without consulting your doctor. Inform any doctor who prescribes medicines for you that you are taking NORVIR. NORVIR oral solution contains alcohol. While taking NORVIR oral solution you should not take medicines that cause a reaction with alcohol such as disulfiram.
Norvir has not specifically been tested for its possible effects on the ability to drive a car or operate machines. As sleepyness and dizziness are known undesira ble effects, Norvir may interfere with the ability to perform potentially hazardous tasks like driving a car or operating heavy machinery. NORVIR oral solution contains 43% alcohol.

HOW DO I TAKE NORVIR? (Posology and Method of Administration)
Always take NORVIR exactly the way your doctor has told you. It is taken by mouth usually two times every day. Your full dose will be 7.5 ml in the morning and 7.5 ml 12 hours later. NORVIR should preferably be taken with food. Like all anti-HIV medications, NORVIR should be taken every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking NORVIR as directed, tell your doctor right away. If you miss a dose, take the missed dose as soon as possible. However, if a dose is skipped, do not double the next dose. Always keep enough NORVIR on hand so you don't run out. When you travel or need to stay in the hospital, make sure you'll have enough NORVIR to last until you can get a new supply. NORVIR oral solution has a lingering aftertaste. You can take it alone or mix it with chocolate milk to improve the taste. NORVIR oral solution has been tested with chocolate milk items to be sure you'll get the right dose when they're mixed. Mix only one dose at a time, and be sure to take the whole dose right away. You shouldn't mix NORVIR with anything else without talking to your doctor or pharmacist. Do not mix with water. Eating salty foods or drinking fluids before or after taking NORVIR oral solution may help clear the aftertaste from your mouth.

HOW DO I MEASURE THE CORRECT DOSE OF THE SOLUTION?
Open the child-proof cap by pushing down on it with your palm and twisting it counterclockwise, or in the direction of the arrow. Talk to your pharmacist if you have difficulty opening the bottle.
The measuring cup provided has been especially designed to give you the right dose of NORVIR oral solution. This cup, which is attached to the bottle cap, is the only cup you should use to measure your dose.

Place the measuring cup on a flat surface at eye-level. Fill it with NORVIR oral solution to the line marked with your dose. Do not fill the cup to any other dosing line. Do not overfill the cup.

HAVE I TAKEN THE CORRECT DOSE?
Don't worry if a little NORVIR oral solution is left in the measuring cup after you've taken your dose. This is normal. You should always use this special cup to take your NORVIR oral solution to make sure you take the right dose.

Wash the measuring cup with soap and warm water as soon as you can. If you don't have soap and water, wipe the inside of the cup with a clean, dry tissue or cloth, and wash the cup with soap and warm water later. If NORVIR is allowed to dry in the cup, it will turn white, which will make the dosing lines hard to see for your next dose. The orange liquid left in the cup will also turn white when it touches water. The dosing cup is not dishwasher-safe.

WHAT IF I TAKE TOO MUCH? (Overdose)
If you realize you have taken more NORVIR than you were supposed to, contact your doctor right away. If you cannot reach your doctor, go to the emergency room.

WHAT SIDE EFFECTS MIGHT I HAVE WITH NORVIR? (Undesirable Effects)
Side effects have been seen during NORVIR treatment. The most common side effects are upset stomach, vomiting, diarrhea, a tingling sensation or numbness in the hands, feet or around the lips and mouth feeling weak/tired and/or bad taste in the mouth.

Report any problems to your doctor immediately.

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 LONG CAN I KEEP A BOTTLE OF NORVIR? (Shelf-life)
A bottle of NORVIR oral solution is good for 30 days after it is opened whether it is in the refrigerator or at room temperature. If the bottle is unopened and kept in the refrigerator, NORVIR is good until the expiration date on the bottle. Do not take NORVIR after the expiration date or from a bottle which has been opened for more than 30 days.
Write down the date when you first open the bottle of NORVIR oral solution.

HOW SHOULD I STORE NORVIR? (Special Precautions for Storage)
Bottles of NORVIR oral solution can be kept in a refrigerator (2 to 8 degrees C) or at room temperature (below 30 degrees C) for 30 days. Don't store NORVIR oral solution in extreme heat or cold (such as in a car during hot or very cold weather, or in your freezer).
It is important to keep NORVIR in the bottle it came in. Don't transfer it to any other container.
As with all medicines, keep NORVIR out of the reach of children.
The marketing authorization holder and the manufacturer for Norvir is:

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL United Kingdom

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

**Belgique/België**  
Parc Scientifique  
Rue du Bosquet, 2  
B-1348 Ottignies/Louvain-la-Neuve  
Belgium  
Tel: (32 10) 475-311

**Italia**  
I 04010 Campoverde di Aprilia  
(Latina) Italy  
Tel: (39-6) 928921

**Luxembourg**  
(se référer à la Belgique/België)

**Danmark**  
Bygstubben 15, Trorod  
DK-2950 VEDBAEK  
Denmark  
Tel: (45-45) 67-01-00

**Nederland**  
Maalderij 21  
1185 ZB Amstelveen  
Tel: (31-20) 545-400

**Österreich**  
Diefenbachgasse 35  
A-1150 Vienna, Austria  
Tel: (43-1) 891-22

**Portugal**  
Rua de Córdova, 1-A  
Alfragide  
2720 Amadora, Portugal  
Tel: (351-1) 471-6903

**Suomi**  
Information Office  
Vapaalantie 2 A  
SF-01650 VANTAA  
Finland  
Tel: (358-0) 853-4022

**Sverige**  
Torshammsgatan 24  
Kista, Stockholm  
Sweden  
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**United Kingdom**  
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NORVIR (ritonavir) capsules 100 mg

WHAT MEDICATION HAS BEEN PRESCRIBED? (Name of the Medicinal Product and Composition)
Each NORVIR (ritonavir) capsule contains 100 mg of ritonavir dissolved in alcohol, polyoxyl 35 castor oil and propylene glycol. Other ingredients include saturated polyglycolyzed glycerides, medium chain triglycerides, polysorbate 80 and anhydrous citric acid. The banding components are gelatine and polysorbate 80. The printing ingredients are shellac, blue 2 and titanium dioxide.

HOW IS NORVIR SUPPLIED? (Pharmaceutical Forms)
NORVIR capsules come in a bottle containing 84 capsules. 4 bottles are provided in one package. Each capsule contains 100 mg of ritonavir.
NORVIR is also supplied as an oral solution containing 80 mg/ml of ritonavir.

WHAT IS NORVIR? (Pharmaco-Therapeutic Group)
NORVIR is an inhibitor of the human immunodeficiency virus (HIV) protease enzyme. It helps control HIV infection by inhibiting or interfering with the protease enzyme that HIV needs to infect new cells.

WHO SHOULD I CALL IF I HAVE QUESTIONS ABOUT NORVIR?
If you have questions about NORVIR, ask your doctor or pharmacist or contact the local representative as listed at the end of this leaflet. Discuss all questions about your health with your doctor.

WHY IS NORVIR BEING PRESCRIBED FOR ME? (Therapeutic Indications)
Your doctor has prescribed NORVIR to help control your HIV infection. NORVIR does this by slowing the spread of infection in your body.
Complete information on the clinical effects of Norvir is not yet available but further studies are in progress.
NORVIR can be given with certain other anti-HIV medicines. There is limited information on the use of Norvir with other drugs. Your doctor will determine which medicines are best for you.

IS THERE ANYONE WHO SHOULDN'T TAKE NORVIR? (Contra-indications)
People who are allergic to NORVIR or any of its ingredients should not take NORVIR.
Pregnant or nursing mothers should not take NORVIR unless specifically directed by their doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are nursing a baby. Health experts recommend that HIV-infected women should not breast feed their infants to avoid transmission of HIV.
Children younger than 12 years of age should not take NORVIR unless specifically directed by their doctor.
People with severe liver disease should not take NORVIR.
While taking NORVIR you **must not** take astemizole or terfenadine which are medicines commonly used to treat allergy symptoms and may be available without a prescription. While taking NORVIR you **must not** take alprazolam, amiodarone, bepridil, bupropion, clorazepate, clozapine, diazepam, encaimide, estazolam, flecainide, flurazepam, meperidine, midazolam, pimozone, piroxicam, propafenone, propoxyphene, quinidine, rifabutin, triazolam or zolpidem. If you're currently taking any of these medicines, ask your doctor about switching to a different medicine while you're taking NORVIR. Often, there are other drugs you can take instead.

Norvir may interact with certain other medications with potential clinical consequences. The use of the following drugs together with Norvir should only take place on the basis of medical advice: immunosuppressants (e.g., cyclosporine, tacrolimus), macrolide antibiotics (e.g., erythromycin, clarithromycin), various steroids (e.g., dexamethasone, prednisolone, ethinyl estradiol), other HIV- protease inhibitors, nonsedating antihistamines (e.g., loratidine), calcium channel antagonists, several tricyclic antidepressants (e.g., desipramine, imipramine, amitriptyline, nortriptyline), other antidepressants (e.g., fluoxetine, paroxetine, sertraline), neuroleptics (e.g., haloperidol, risperidone, thioridazine), antifungals (e.g., ketoconazole, itraconazole), morphinomimetics (e.g., methadone, fentanyl), carbamazepine, warfarin, tolbutamide, theophylline.

Be sure to tell your doctor about **all** of the medicines you're taking, even those that do not require a prescription.

**WHAT ELSE SHOULD I KNOW ABOUT NORVIR?** (Special Precautions for Use)

Even if you feel better, do not stop taking NORVIR without talking to your doctor.

NORVIR has not been shown to lower the risk of passing HIV to others through sexual contact or blood transfer. You should use appropriate precautions.

People with liver disease who take NORVIR may need additional testing. Your doctor will decide if this is needed for you.

Using NORVIR as recommended should give you the best chance to delay the development of drug resistance.

You should not take any OTC (over the counter) medicine without consulting your doctor. Inform any doctor prescribing medicines for you that you are taking NORVIR.

Norvir has not specifically been tested for its possible effects on the ability to drive a car or operate machines. As sleepyness and dizziness are known undesirable effects, Norvir may interfere with the ability to perform potentially hazardous tasks like driving a car or operating heavy machinery.

**HOW DO I TAKE NORVIR?** (Posology and Method of Administration)

Always take NORVIR exactly the way your doctor has told you. It is taken by mouth usually two times every day. Your full dose will be 6 capsules in the morning, then 6 capsules 12 hours later.

NORVIR should preferably be taken with food.

Like all anti-HIV medications, NORVIR should be taken every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking NORVIR as directed, tell your doctor right away.

If you miss a dose, take the missed dose as soon as possible. However, if a dose is skipped, do not double the next dose.

Always keep enough NORVIR on hand so you don't run out. When you travel or need to stay in the hospital, make sure you'll have enough NORVIR to last until you can get a new supply.

**WHAT IF I TAKE TOO MUCH?** (Overdose)
If you realize you have taken more NORVIR than you were supposed to, contact your doctor right away. If you cannot reach your doctor, go to the emergency room.

**WHAT SIDE EFFECTS MIGHT I HAVE WITH NORVIR? (Undesirable Effects)**

Side effects have been seen during NORVIR treatment. The most common side effects are upset stomach, vomiting, diarrhea, a tingling sensation or numbness in the hands, feet or around the lips or mouth, feeling weak/tired and/or bad taste in the mouth.

Report any problems to your doctor immediately.

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 LONG CAN I KEEP NORVIR? (Shelf-life)**

Do not take NORVIR after the expiration date shown on the bottle.

**HOW SHOULD I STORE NORVIR? (Special Precautions for Storage)**

NORVIR capsules must be kept in a refrigerator.

Don't store NORVIR capsules in extreme heat or cold (such as in a car during hot or very cold weather, or in your freezer).

It is important to keep NORVIR in the bottle it came in. Don't transfer it to any other container.

As with all medicines, keep NORVIR out of the reach of children.

**Marketing authorization holder for Norvir is:**

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

**The manufacturers for NORVIR are:**

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

Abbott Laboratories S.A.
c/Josefa Valcárcel 48
28027 Madrid
Spain.

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

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