

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kaletra soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Kaletra soft capsule contains 133.3 mg of lopinavir co-formulated with 33.3 mg of ritonavir as a pharmacokinetic enhancer.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsules.

The capsules are orange with a black ink imprint of [Abbott logo] and “PK”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kaletra is indicated for the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents.

Most experience with Kaletra is derived from the use of the product in antiretroviral therapy naïve patients. Data in heavily pretreated protease inhibitor experienced patients are limited. There are limited data on salvage therapy on patients who have failed with Kaletra.

The choice of Kaletra to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see sections 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Kaletra should be prescribed by physicians who are experienced in the treatment of HIV infection.

Adult and adolescent use: the recommended dosage of Kaletra is three capsules twice daily taken with food. Oral solution is available to patients who have difficulty swallowing.

Paediatric use (2 years of age and above): the recommended dosage of Kaletra for children with a Body Surface Area of 1.3 m² or greater, is 3 capsules twice daily taken with food. For children with a Body Surface Area* of less than 1.3 m², use of Kaletra oral solution is recommended (please refer to Kaletra oral solution Summary of Product Characteristics).

* Body surface area can be calculated with the following equation

$$\text{BSA (m}^2\text{)} = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)}) / 3600}$$

Children less than 2 years of age: Kaletra is not recommended for use in children less than 2 years of age because of limited efficacy and safety data.

Hepatic impairment: Kaletra should be used with caution in patients with mild to moderate hepatic insufficiency. Kaletra should not be given to patients with severe hepatic insufficiency (see sections 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

Renal impairment: No dose adjustment is necessary in patients with renal impairment. Caution is warranted when Kaletra is used in patients with severe renal impairment (see section 4.4 Special warnings and special precautions for use).

4.3 Contraindications

Patients with known hypersensitivity to lopinavir, ritonavir or any of the excipients.

Patients with severe hepatic insufficiency.

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Kaletra should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include astemizole, terfenadine, midazolam, triazolam, cisapride, pimozide, amiodarone, ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine).

Kaletra also inhibits CYP2D6 *in vitro* but to a lesser extent than CYP3A. The clinical relevance of this inhibition has not been investigated. Pending further information, Kaletra should not be co-administered with medicinal products that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include flecainide and propafenone (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Patients on Kaletra should not use products containing St John's wort (*Hypericum perforatum*) because co-administration may be expected to reduce plasma concentrations of Kaletra. This may result in loss of therapeutic effect and development of resistance (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Rifampicin should not be used in combination with Kaletra because co-administration may cause large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect (see section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and special precautions for use

Patients with coexisting conditions

Lopinavir and ritonavir are primarily metabolised and eliminated by the liver, and increased plasma concentrations are expected in patients with hepatic impairment. There are no data available from these patients and specific dosage recommendations cannot be made (see section 4.3 Contraindications).

Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C; therefore, caution must be exercised when administering Kaletra.

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

Lipid elevations

Treatment with Kaletra has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing is to be performed prior to initiating Kaletra therapy and at periodic intervals during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders are to be managed as clinically appropriate (see also section 4.5 Interaction with other medicinal products and other forms of interaction for additional information on potential interactions with HMG-CoA reductase inhibitors).

Pancreatitis

Cases of pancreatitis have been reported in patients receiving Kaletra, including those who developed hypertriglyceridaemia. In most of these cases patients have had a prior history of pancreatitis and/or concurrent therapy with other medicinal products associated with pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Kaletra therapy should be suspended if a diagnosis of pancreatitis is made (see section 4.8 Undesirable effects).

Hyperglycaemia

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

Fat redistribution & metabolic disorders

Combination antiretroviral therapy, including regimens containing a protease inhibitor, has been associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of serum lipids and blood glucose. The mechanisms of these events and long

term consequences, such as an increased risk of cardiovascular disease, are currently unknown (see section 4.8 Undesirable effects).

Interactions with medicinal products

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A, and to a lesser extent CYP2D6. Kaletra is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A, and may result in increased plasma concentrations of medicinal products that are primarily metabolised by CYP2D6. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events (see sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction).

Particular caution must be used when prescribing sildenafil in patients receiving Kaletra. Co-administration of Kaletra with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see section 4.5 Interaction with other medicinal products and other forms of interaction).

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of Kaletra with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if Kaletra is used concurrently with atorvastatin or cerivastatin, which are metabolised to a lesser extent by CYP3A4. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Particular caution must be used when prescribing Kaletra and medicinal products known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin, clarithromycin. Indeed, Kaletra could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse events. Cardiac events have been reported with Kaletra in preclinical studies; therefore, the potential cardiac effects of Kaletra cannot be currently ruled out (see sections 4.8 Undesirable effects, and 5.3 Preclinical safety data).

Rifampicin should not be used in combination with Kaletra because this may cause large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect (see sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interactions).

Oral Contraceptives: since levels of ethinyl oestradiol may be decreased alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives are co-administered (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Other

Kaletra is not recommended for use in children less than 2 years of age because of limited efficacy and safety data.

Kaletra is not a cure for HIV infection or AIDS. It does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Appropriate precautions should be taken. People taking Kaletra may still develop infections or other illnesses associated with HIV disease and AIDS.

There are limited data on salvage therapy on patients who have failed with Kaletra. There are ongoing studies to further establish the usefulness of potential salvage therapy regimens (e.g. amprenavir or saquinavir). There are currently limited data on the use of Kaletra in protease inhibitor-experienced patients.

Kaletra soft capsules contain sunset yellow [E110] as an excipient, which can cause allergic-type reaction. Allergy is more common in those people who are allergic to aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A *in vitro*. Co-administration of Kaletra and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. Kaletra inhibits CYP2D6 *in vitro* but to a lesser extent than CYP3A. The clinical relevance of this inhibition has not been investigated. Kaletra does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations (see section 4.3 Contraindications).

Kaletra has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450 enzymes and by glucuronidation. This may result in lowered plasma concentrations and potential decrease of efficacy of co-administered medicinal products.

Medicinal products that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in section 4.3 Contraindications.

Antiretroviral agents

Nucleoside reverse transcriptase inhibitors (NRTIs):

Stavudine and Lamivudine: no change in the pharmacokinetics of lopinavir was observed when Kaletra was given alone or in combination with stavudine and lamivudine in clinical studies.

Didanosine: it is recommended that didanosine be administered on an empty stomach; therefore, didanosine is to be given one hour before or two hours after Kaletra (given with food). The gastroresistant formulation of didanosine should be administered at least two hours after a meal.

Zidovudine and Abacavir: Kaletra induces glucuronidation, therefore Kaletra has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Nevirapine: no change in the pharmacokinetics of lopinavir was apparent in healthy volunteers during nevirapine and Kaletra co-administration. Results from a study in HIV-positive paediatric patients revealed a decrease in lopinavir concentrations during nevirapine co-administration. The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric patients and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic interaction is unknown. No formal recommendation

could be drawn on dosage adjustment when Kaletra is used in combination with nevirapine. However, based on clinical experience, Kaletra dose increase to 533/133 mg (4 capsules) twice daily may be considered when co-administered with nevirapine, particularly for patients in whom reduced lopinavir susceptibility is likely.

Efavirenz: when used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced patients, increasing the dose of Kaletra 33.3 % from 400/100 mg (3 capsules) twice daily to 533/133 mg (4 capsules) twice daily yielded similar lopinavir plasma concentrations as compared to historical data of Kaletra 400/100 mg (3 capsules) twice daily.

Dosage increase of Kaletra from 400/100 mg (3 capsules) twice daily to 533/133 mg (4 capsules) twice daily should be considered when co-administered with efavirenz. Caution is warranted since this dosage adjustment might be insufficient in some patients.

Protease inhibitors (PIs):

Kaletra is expected to increase concentrations of the HIV-protease inhibitors indinavir, nelfinavir and saquinavir. The pharmacokinetics of single-dose indinavir and saquinavir obtained in healthy volunteers after at least 10 days of Kaletra 400/100 mg twice daily were compared to historical data in HIV-infected patients. Because of limitations in the study design it is not possible to make definitive dosing recommendations. However, based on these comparisons, indinavir 600 mg twice daily and saquinavir 800 mg twice daily, when co-administered with Kaletra 400/100 mg twice daily, may produce a similar AUC and higher C_{min} relative to its respective established clinical dosing regimen. When co-administered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33 % and C_{min} increased 64 % as compared to Kaletra 400/100 mg (3 capsules) twice daily. Appropriate doses of HIV-protease inhibitors in combination with Kaletra with respect to safety and efficacy have not been established.

Other medicinal products:

Antiarrhythmics (bepridil, systemic lidocaine and quinidine): concentrations may be increased when co-administered with Kaletra. Caution is warranted and therapeutic concentration monitoring is recommended when available.

Anticoagulants: Warfarin concentrations may be affected when co-administered with Kaletra. It is recommended that INR (international normalised ratio) be monitored.

Anticonvulsants (phenobarbital, phenytoin, carbamazepine): will induce CYP3A4 and may decrease lopinavir concentrations.

Dihydropyridine calcium channel blockers (e.g. felodipine, nifedipine, nicaldipine): may have their serum concentrations increased by Kaletra.

HMG-CoA reductase inhibitors: HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with Kaletra. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with Kaletra is not recommended. Atorvastatin and cerivastatin are less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with Kaletra, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with Kaletra, the lowest possible doses of atorvastatin and cerivastatin should be administered. Results from an interaction study with Kaletra and pravastatin reveal no clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with Kaletra. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Dexamethasone: may induce CYP3A4 and may decrease lopinavir concentrations.

Sildenafil: co-administration of sildenafil 100 mg single dose with ritonavir 500 mg twice daily at steady-state resulted in a 1000 % increase in sildenafil plasma AUC. On the basis of these data, concomitant use of sildenafil with Kaletra is not recommended and in no case should the starting dose of sildenafil exceed 25 mg within 48 hours (see section 4.4 Special warnings and special precautions for use).

Cyclosporin and tacrolimus: concentrations may be increased when co-administered with Kaletra. More frequent therapeutic concentration monitoring is recommended until plasma levels of these products have been stabilised.

Ketoconazole and itraconazole: may have serum concentrations increased by Kaletra. High doses of ketoconazole and itraconazole (> 200 mg/day) are not recommended.

Clarithromycin: moderate increases in clarithromycin AUC are expected when co-administered with Kaletra. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered (see section 4.4 Special warnings and special precautions for use).

Methadone: Kaletra was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives: since levels of ethinyl oestradiol may be decreased alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives are co-administered.

Rifabutin: when rifabutin and Kaletra were co-administered for 10 days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or 3 times per week) is recommended when administered with Kaletra. Further reduction may be necessary.

Rifampicin: due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with Kaletra (see sections 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

St John's wort: patients on Kaletra should not use concomitantly products containing St John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of Kaletra. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see section 4.3 Contraindications).

Based on known metabolic profiles, clinically significant interactions are not expected between Kaletra and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.

4.6 Pregnancy and lactation

There are no data from the use of Kaletra in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The potential risk for humans is unknown. Kaletra should not be used during pregnancy unless clearly necessary.

Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. HIV infected women must not breast-feed their infants under any circumstances to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive a car and use machines have been performed.

4.8 Undesirable effects

The safety of Kaletra has been investigated in 612 patients in Phase II/III clinical trials, of which 442 have received a dose of 400/100 mg (3 capsules) twice daily. In some studies, Kaletra was used in combination with efavirenz or nevirapine.

The most common adverse event associated with Kaletra therapy was diarrhoea occurring in approximately 14 % of patients and which was generally of mild to moderate severity. Discontinuation due to adverse reactions was 2.5 % (naïve patients) and 8 % (experienced patients) over a 24 week period.

It is important to note that cases of pancreatitis have been reported in patients receiving Kaletra, including those who developed hypertriglyceridaemia. Furthermore, rare increases in PR interval have been reported during Kaletra therapy (see section 4.4 Special warnings and special precautions for use: sections pancreatitis and lipids).

ADULT PATIENTS

Adverse events (≥ 2 % patients):

The following adverse reactions of moderate to severe intensity with possible or probable relationship to Kaletra have been reported in $\geq 2\%$ of patients: diarrhoea 14 %, nausea 6 %, vomiting 2 %, abdominal pain 2.5 %, asthenia 4 % and headache 3 %.

Laboratory Abnormalities

Marked clinical laboratory abnormalities (Grade 3 or 4) reported in $\geq 2\%$ of patients included: increased glucose (2.5 %), increased SGOT/AST (2 %), increased SGPT/ALT (2 %) increased GGT (9 %), increased total cholesterol (8.5 %) and increased triglycerides (8 %) (see section 4.4 Special warnings and special precautions for use: pancreatitis and lipids). For lipids elevations, each of these reactions is considered common.

Adverse events (1 - 2 % patients):

Rash, abnormal stools, insomnia are considered common (occurrence 1 – 2 %).

Adverse events (< 1 % patients) listed below by body system:

Haemic and Lymphatic System: anaemia, leucopenia, and lymphadenopathy.

Endocrine System: Cushing's syndrome and hypothyroidism.

Metabolic and Nutritional Disorders: avitaminosis, dehydration, oedema, decreased glucose tolerance, lactic acidosis, obesity, peripheral oedema, and weight loss.

Nervous System: abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, dyskinesia, emotional lability, encephalopathy, hypertonia, insomnia, decreased libido, nervousness, neuropathy, paresthesia, peripheral neuritis, somnolence, abnormal thinking, and tremor.

Special Senses: abnormal vision, eye disorder, otitis media, taste perversion, and tinnitus.

Cardiovascular System: hypertension, palpitation, thrombophlebitis, and vasculitis.

Respiratory System: bronchitis, dyspnea, lung oedema, and sinusitis.

Digestive System: abnormal stools, anorexia, cholecystitis, constipation, dry mouth, dyspepsia, dysphagia, enterocolitis, eructation, oesophagitis, faecal incontinence, flatulence, gastrointestinal disorder, gastritis, gastroenteritis, haemorrhagic colitis, increased appetite, pancreatitis (see section 4.4 Special warnings and special precautions for use: pancreatitis and lipids), sialadenitis, stomatitis, and ulcerative stomatitis.

Skin and Appendages: acne, alopecia, dry skin, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, skin benign neoplasm, skin discoloration and sweating.

Musculoskeletal System: arthralgia, arthrosis and myalgia.

Urogenital System: abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, and urine abnormality.

Others: back pain, chest pain, chest pain substernal, chills, cyst, face oedema, fever, flu syndrome and malaise.

PAEDIATRIC PATIENTS

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults. Rash (2 %) was the only drug-related clinical adverse event of moderate or severe intensity in $\geq 2\%$ of paediatric patients treated with combination therapy including Kaletra for up to 24 weeks. In 1 % of paediatric patients: allergic reaction, constipation, dry skin, fever, hepatomegaly, taste perversion and vomiting were reported.

Marked clinical laboratory abnormalities (Grade 3 or 4) reported in $\geq 2\%$ of paediatric patients included: high bilirubin (3%), high SGPT/ALT (4%), high SGOT/AST (7%), high total cholesterol (2%), high amylase (4%), low sodium (3%), low platelets (4%) and low neutrophils (2%). Each of these reactions is considered common.

Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

Combination antiretroviral therapy, including regimens containing a protease inhibitor, has been associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of serum lipids and blood glucose. The mechanisms of these events and long term consequences, such as an increased risk of cardiovascular disease, are currently unknown (see section 4.4 Special warnings and special precautions for use).

4.9 Overdose

To date, there is limited human experience of acute overdose with Kaletra.

The adverse clinical signs observed in dogs included salivation, emesis and diarrhoea/abnormal stool. The signs of toxicity observed in mice, rats or dogs included decreased activity, ataxia, emaciation, dehydration and tremors.

There is no specific antidote for overdose with Kaletra. Treatment of overdose with Kaletra is to consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since Kaletra is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antiviral for systemic use, ATC code: J05A

Mechanism of action: Lopinavir provides the antiviral activity of Kaletra. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral activity *in vitro*: the *in vitro* antiviral activity of lopinavir against laboratory and clinical HIV strains was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean EC_{50} of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50% human serum, the mean EC_{50} of lopinavir against HIV-1_{IIIIB} in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean EC_{50} of lopinavir was 6.5 nM against several HIV-1 clinical isolates.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. HIV-1 has been passaged *in vitro* with lopinavir alone and with lopinavir plus ritonavir at concentration ratios representing the range of plasma concentration ratios observed during Kaletra therapy. Genotypic and phenotypic analysis of viruses selected in these passages suggest that the presence of ritonavir, at these concentration ratios, does not measurably influence the selection of lopinavir-resistant viruses. Overall, the *in vitro* characterisation of phenotypic cross-resistance between lopinavir and other protease inhibitors suggest that decreased susceptibility to lopinavir correlated closely with decreased susceptibility to ritonavir and indinavir, but did not correlate closely with decreased susceptibility to amprenavir, saquinavir, and nelfinavir.

Genotypic correlates of reduced phenotypic susceptibility to lopinavir in viruses selected by other protease inhibitors. The *in vitro* antiviral activity of lopinavir against 112 clinical isolates taken from patients failing therapy with one or more protease inhibitors was assessed. Within this panel, the following mutations in HIV protease were associated with reduced *in vitro* susceptibility to lopinavir: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M. The median EC₅₀ of lopinavir against isolates with 0 - 3, 4 - 5, 6 - 7 and 8 - 10 mutations at the above amino acid positions was 0.8, 2.7, 13.5 and 44.0-fold higher than the EC₅₀ against wild type HIV, respectively. The 16 viruses that displayed > 20-fold change in susceptibility all contained mutations at positions 10, 54, 63 plus 82 and/or 84. In addition, they contained a median of 3 mutations at amino acid positions 20, 24, 46, 53, 71 and 90.

Antiviral activity of Kaletra in patients failing protease inhibitor therapy. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to Kaletra therapy, with respect to baseline viral genotype and phenotype, in 56 patients previously failing therapy with multiple protease inhibitors. The EC₅₀ of lopinavir against the 56 baseline viral isolates ranged from 0.6 to 96-fold higher than the EC₅₀ against wild type HIV. After 24 weeks of treatment with Kaletra, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤ 400 copies/ml was observed in 93 % (27/29), 78 % (7/9), 67 % (4/6) and 50 % (4/8) patients with < 10-fold, 10 to 20-fold, 20 to 40-fold, and > 40-fold reduced susceptibility to lopinavir at baseline, respectively. In addition, virologic response was observed in 96 % (24/25), 76 % (16/21) and 33 % (2/6) patients with 0 - 5, 6 - 7, and 8 - 10 mutations of the above mutations in HIV protease associated with reduced *in vitro* susceptibility to lopinavir. Since these patients had not previously been exposed to either Kaletra or efavirenz, part of the response may be attributed to the antiviral activity of efavirenz, particularly in patients harbouring highly lopinavir resistant virus. The study did not contain a control arm of patients not receiving Kaletra.

Selection of viral resistance during Kaletra therapy. In Phase II studies of 227 antiretroviral treatment naïve and protease inhibitor experienced patients, isolates from four patients with quantifiable (> 400 copies/ml) viral load following treatment with Kaletra for ≥ 12 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. The mean EC₅₀ of lopinavir against the four baseline isolates was 2.8 fold (range: 0.7 to 5.2 fold) higher than the EC₅₀ against wild type HIV, and each of the four baseline isolates contained four or more mutations in HIV protease associated with resistance to protease inhibitors. Following treatment of the four patients with Kaletra, the mean EC₅₀ of lopinavir increased to 55-fold (range: 9.4 to 99-fold) compared to wild type HIV, and 2 - 3 additional mutations at amino acids 10, 24, 33, 46, 54, 63, 71 and/or 82 were observed.

Cross-resistance: at this stage of development, little information is available on the cross-resistance of viruses selected during therapy with Kaletra. Isolates from 4 patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during Kaletra therapy either remained or developed cross-resistance to ritonavir, indinavir, and nelfinavir. All rebound viruses either remained fully sensitive or demonstrated modestly reduced susceptibility to amprenavir (up to 8.6-fold concurrent with 99-fold

resistance to lopinavir). The rebound isolates from the two patients with no prior saquinavir treatment remained fully sensitive to saquinavir.

Clinical pharmacodynamic data

The effects of Kaletra (in combination with other antiretroviral agents) on biological markers (plasma HIV RNA levels and CD₄ counts) have been investigated in a controlled study of Kaletra of 24 weeks duration, and in additional studies of Kaletra of 72 weeks duration.

Adult Use

Patients without prior antiretroviral therapy

Study M98-863 is a randomised, double-blind trial of 653 antiretroviral treatment naïve patients investigating Kaletra (400/100 mg twice daily) compared to nelfinavir (750 mg three times daily) plus nucleoside reverse transcriptase inhibitors. By intent to treat analysis where patients with missing values are considered virologic failures, the proportion of patients at 24 weeks with HIV RNA < 400 copies/ml in the Kaletra arm was 79 % and 71 % in the nelfinavir arm. Mean baseline CD₄ cell count was 259 cells/mm³ (range: 2 to 949 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/ml (range: 2.6 to 6.8 log₁₀ copies/ml). Through 24 weeks of therapy, the proportion of patients in the Kaletra arm with plasma RNA < 50 copies/ml was 65 % and 60 % in the nelfinavir arm. The mean increase from baseline in CD₄ cell count was 154 cells/mm³ in the Kaletra arm and 150 cells/mm³ in the nelfinavir arm. Preliminary data at 48 weeks suggest that the virological response is sustained at long-term.

Sustained virological response to Kaletra (in combination with lamivudine and stavudine) has been also observed in a small Phase II study (M97-720) through 72 weeks of treatment.

Patients with prior antiretroviral therapy

Study M97-765 is a randomised, double-blind trial evaluating Kaletra at two dose levels (400/100 mg and 400/200 mg, both twice daily) plus nevirapine (200 mg twice daily) and two nucleoside reverse transcriptase inhibitors in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor naïve patients. Median baseline CD₄ cell count was 349 cells/mm³ (range 72 to 807 cells/mm³) and median baseline plasma HIV-1 RNA was 4.0 log₁₀ copies/ml (range 2.9 to 5.8 log₁₀ copies/ml). By intent to treat analysis where patients with missing values are considered virologic failures, the proportion of patients with HIV RNA < 400 (< 50) copies/ml at 24 weeks was 75 % (58 %) and the mean increase from baseline in CD₄ cell count was 174 cells/mm³ for the 36 patients receiving the 400/100 mg dose of Kaletra.

M98-957 is a randomised, open-label study evaluating Kaletra treatment at two dose levels (400/100 mg and 533/133 mg, both twice daily) plus efavirenz (600 mg once daily) and nucleoside reverse transcriptase inhibitors in 57 multiple protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor naïve patients. Median baseline CD₄ cell count was 220 cells/mm³ (range 13 to 1030 cells/mm³). By intent to treat analysis where patients with missing values are considered virologic failures, the proportion of patients with HIV RNA < 400 copies/ml at 24 weeks was 69 % and 82 % and the mean increase from baseline CD₄ cell count was 48 cells/mm³ and 41 cells/mm³ for patients receiving the 400/100 mg dose (n=29) and the 533/133 mg dose (n=28) of Kaletra, respectively.

Paediatric Use

M98-940 is an open-label study of a liquid formulation of Kaletra in 100 antiretroviral naïve (44 %) and experienced (56 %) paediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomised to either 230 mg lopinavir/57.5 mg ritonavir per m² or 300 mg lopinavir/75 mg ritonavir per m². Naïve patients also received nucleoside reverse transcriptase inhibitors. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors. Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after 3 weeks of therapy in each patient. Subsequently, all patients were continued on the 300/75 mg per m² dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14 patients less than 2 years old and 6 patients one year or less. Mean baseline CD₄ cell count was 838 cells/mm³ and mean baseline plasma HIV-1 RNA was 4.7 log₁₀ copies/ml. Through 24 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/ml was 82 % for antiretroviral naïve patients and 66 % for antiretroviral experienced patients and the mean increase from baseline in CD₄ cell count was 328 cells/mm³ and 335 cells/mm³ respectively.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of Kaletra 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15 to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7 % of those obtained after the ritonavir dose of 600 mg twice daily. The *in vitro* antiviral EC₅₀ of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Absorption: multiple dosing with 400/100 mg Kaletra twice daily for 3 to 4 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption: Kaletra soft capsules and liquid have been shown to be bioequivalent under nonfasting conditions (moderate fat meal). Administration of a single 400/100 mg dose of Kaletra soft capsules with a moderate fat meal (500 – 682 kcal, 22.7 % to 25.1 % from fat) was associated with a mean increase of 48 % and 23 % in lopinavir AUC and C_{max}, respectively, relative to fasting. For Kaletra oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 % and 54 %, respectively. Administration of Kaletra with a high fat meal (872 kcal, 55.8 % from fat) increased lopinavir AUC and C_{max} by 96 % and 43 %, respectively, for soft capsules, and 130 % and 56 %, respectively, for oral solution. To enhance bioavailability and minimise variability Kaletra is to be taken with food.

Distribution: at steady state, lopinavir is approximately 98 - 99 % bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg Kaletra twice daily, and is similar between healthy volunteers and HIV-positive patients.

Metabolism: *in vitro* experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir and therefore, increases plasma levels of lopinavir. A ¹⁴C-lopinavir study in humans showed that 89 % of the plasma radioactivity after a single 400/100 mg Kaletra dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but comprise only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 days to 2 weeks.

Elimination: after a 400/100 mg ¹⁴C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3 % and 82.6 ± 2.5 % of an administered dose of ¹⁴C-lopinavir can be accounted for in urine and faeces, respectively. Unchanged lopinavir accounted for approximately 2.2 % and 19.8 % of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3 % of the lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of lopinavir over a 12 hour dosing interval averaged 5 - 6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 l/h.

Special Populations

Paediatrics: there are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of Kaletra 300/75 mg/m² twice daily and 230/57.5 mg/m² twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 µg•h/ml, 8.2 ± 2.9 µg/ml and 3.4 ± 2.1 µg/ml, respectively after Kaletra 230/57.5 mg/m² twice daily without nevirapine (n=12), and were 85.8 ± 36.9 µg•h/ml, 10.0 ± 3.3 µg/ml and 3.6 ± 3.5 µg/ml, respectively after 300/75 mg/m² twice daily with nevirapine (n=12). The 230/57.5 mg/m² twice daily regimen without nevirapine and the 300/75 mg/m² twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine. Kaletra soft capsules and Kaletra oral solution are bioequivalent under nonfasting conditions.

Gender, Race and Age: Kaletra pharmacokinetics have not been studied in the elderly. No age or gender related pharmacokinetic differences have been observed in adult patients. Pharmacokinetic differences due to race have not been identified.

Renal Insufficiency: Kaletra pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency: Kaletra is principally metabolised and eliminated by the liver. Kaletra has not been studied in patients with hepatic insufficiency (see sections 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

5.3 Preclinical safety data

Repeat-dose toxicity studies in rodents and dogs identified major target organs as the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular

swelling with focal degeneration. While exposure eliciting these changes were comparable to or below human clinical exposure, dosages in animals were over 6-fold the recommended clinical dose. Mild renal tubular degeneration was confined to mice exposed with at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not other species. Serum cholesterol was elevated in rodents but not dogs, while triglycerides were elevated only in mice.

In dogs, prominent U waves on the electrocardiogram have been observed associated with prolonged PR interval and bradycardia. These effects have been assumed to be caused by electrolytic disturbance. However, these observations cannot rule out any potential cardiac effects of the medicinal product in humans (see also sections 4.4 Special warnings and special precautions for use, and 4.8 Undesirable effects).

In rats, embryofetotoxicity (pregnancy loss, decreased foetal viability, decreased foetal body weights, increased frequency of skeletal variations) and postnatal developmental toxicity (decreased survival of pups) was observed at maternally toxic dosages. The systemic exposure to lopinavir/ritonavir at the maternal and developmental toxic dosages was lower than the intended therapeutic exposure in humans.

Long-term carcinogenicity studies of lopinavir/ritonavir in animal systems have not been completed. However, lopinavir/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, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

oleic acid,
propylene glycol,
polyoxyl 35 castor oil,
purified water

Capsule shell:

gelatine,
anhydriized liquid sorbitol (mixture of sorbitol, sorbitol anhydrides and mannitol),
glycerol,
titanium dioxide (E171),
sunset yellow (E110)
medium-chain triglycerides,
lecithin

Black ink containing:

propylene glycol,
black iron oxide (E172),

polyvinyl acetate phthalate,
polyethylene glycol 400,
ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store Kaletra soft capsules at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

6.5 Nature and content of container

High density polyethylene (HDPE) bottles closed with polypropylene caps. Each bottle contains 90 capsules. Each pack contains 2 bottles (180 capsules).

Blisters consisting of PVC/fluoropolymer foil. Each carton contains 6 foil blisters each containing 6 capsules (36 capsules). Each pack contains 5 cartons (180 capsules).

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Kaletra oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Kaletra oral solution contains 400 mg of lopinavir co-formulated with 100 mg of ritonavir as a pharmacokinetic enhancer.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

The solution is light yellow to golden.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kaletra is indicated for the treatment of HIV-1 infected adults and children above the age of 2 years, in combination with other antiretroviral agents.

Most experience with Kaletra is derived from the use of the product in antiretroviral therapy naïve patients. Data in heavily pretreated protease inhibitor experienced patients are limited. There are limited data on salvage therapy on patients who have failed therapy with Kaletra.

The choice of Kaletra to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see sections 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Kaletra should be prescribed by physicians who are experienced in the treatment of HIV infection.

Adult and adolescent use: the recommended dosage of Kaletra is 5 ml of oral solution (400/100 mg) twice daily taken with food.

Paediatric use (2 years of age and above): the recommended dosage of Kaletra is 230/57.5 mg/m² twice daily taken with food, up to a maximum dose of 400/100 mg twice daily. The 230/57.5 mg/m² dosage might be insufficient in some children when co-administered with nevirapine or efavirenz. An increase of the dose of Kaletra to 300/75 mg/m² should be considered in these patients. Dose should be administered using a calibrated oral dosing syringe.

Paediatric Dosing Guidelines	
Body Surface Area* (m ²)	Twice Daily Dose (230/57.5 mg/m ²)
0.25	0.7 ml (57.5/14.4 mg)
0.50	1.4 ml (115/28.8 mg)
0.75	2.2 ml (172.5/43.1 mg)
1.00	2.9 ml (230/57.5 mg)
1.25	3.6 ml (287.5/71.9 mg)
1.5	4.3 ml (345/86.3 mg)
1.75	5 ml (402.5/100.6 mg)

* Body surface area can be calculated with the following equation

$$BSA (m^2) = \sqrt{(Height (cm) \times Weight (kg) / 3600)}$$

Kaletra is not recommended for use in children less than 2 years of age because of limited safety and efficacy data. Paediatric patients should switch from Kaletra oral solution to soft capsules as soon as they are able to swallow the capsule formulation (see section 4.4 Special warnings and precautions for use).

Hepatic impairment: Kaletra should be used with caution in patients with mild to moderate hepatic insufficiency. Kaletra should not be given to patients with severe hepatic insufficiency (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Renal impairment: No dose adjustment is necessary in patients with renal impairment. Caution is warranted when Kaletra is used in patients with severe renal impairment (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

Patients with known hypersensitivity to lopinavir, ritonavir or any of the excipients.

Patients with severe hepatic insufficiency.

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Kaletra must not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include astemizole, terfenadine, midazolam, triazolam, cisapride, pimozone, amiodarone, ergot alkaloids (e.g. ergotamine, dihydroergotamine and ergonovine and methylergonovine).

Kaletra also inhibits CYP2D6 *in vitro* but to a lesser extent than CYP3A. The clinical relevance of this inhibition has not been investigated. Pending further information, Kaletra should not be co-administered with medicinal products that are highly dependent on CYP2D6 metabolism and for which elevated plasma concentrations are associated with serious and/or life threatening events. These medicinal products include flecainide and propafenone (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Patients on Kaletra should not use products containing St John's wort (*Hypericum perforatum*) because co-administration may be expected to reduce plasma concentrations of

Kaletra. This may result in loss of therapeutic effect and development of resistance (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Kaletra oral solution is contraindicated in children below the age of 2 years, pregnant women, patients with hepatic or renal failure and patients treated with disulfiram or metronidazole due to the potential risk of toxicity from the excipient propylene glycol (see section 4.4 Special warnings and special precautions for use).

Rifampicin should not be used in combination with Kaletra because co-administration may cause large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect (see section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and special precautions for use

Patients with coexisting conditions

Lopinavir and ritonavir are primarily metabolised and eliminated by the liver, and increased plasma concentrations are expected in patients with hepatic impairment. There are no data available from these patients and specific dosage recommendations cannot be made (see section 4.3 Contraindications).

Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C; therefore, caution must be exercised when administering Kaletra.

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

Lipid elevations

Treatment with Kaletra has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing is to be performed prior to initiating Kaletra therapy and at periodic intervals during therapy. Particular caution should be paid to patients with high values at baseline and with history of lipid disorders. Lipid disorders are to be managed as clinically appropriate (see also section 4.5 Interaction with other medicinal products and other forms of interaction for additional information on potential interactions with HMG-CoA reductase inhibitors).

Pancreatitis

Cases of pancreatitis have been reported in patients receiving Kaletra, including those who developed hypertriglyceridaemia. In most of these cases patients have had a prior history of pancreatitis and/or concurrent therapy with other medicinal products associated with

pancreatitis. Marked triglyceride elevation is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Kaletra therapy should be suspended if a diagnosis of pancreatitis is made (see section 4.8 Undesirable effects).

Hyperglycaemia

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

Fat redistribution & metabolic disorders

Combination antiretroviral therapy, including regimens containing a protease inhibitor, has been associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of serum lipids and blood glucose. The mechanisms of these events and long term consequences, such as an increased risk of cardiovascular disease, are currently unknown (see section 4.8 Undesirable effects).

Interactions with medicinal products

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A, and to a lesser extent CYP2D6. Kaletra is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A, and may result in increased plasma concentrations of medicinal products that are primarily metabolised by CPY2D6. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events (see sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction).

Particular caution must be used when prescribing sildenafil in patients receiving Kaletra. Co-administration of Kaletra with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see section 4.5 Interaction with other medicinal products and other forms of interaction).

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of Kaletra with simvastatin or lovastatin is not recommended due to an increased risk of myopathy including rhabdomyolysis. Caution must also be exercised and reduced doses should be considered if Kaletra is used concurrently with atorvastatin or cerivastatin, which are metabolised to a lesser extent by CYP3A4. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Particular caution must be used when prescribing Kaletra and medicinal products known to induce QT interval prolongation such as: chlorpheniramine, quinidine, erythromycin,

clarithromycin. Indeed, Kaletra could increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac adverse events. Cardiac events have been reported with Kaletra in preclinical studies; therefore, the potential cardiac effects of Kaletra cannot be currently ruled out (see sections 4.8 Undesirable effects, and 5.3 Preclinical safety data).

Rifampicin should not be used in combination with Kaletra because this may cause large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect (see sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interactions).

Oral Contraceptives: since levels of ethinyl oestradiol may be decreased alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives are co-administered (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Other

Patients taking the oral solution, particularly those with renal impairment or with decreased ability to metabolise propylene glycol (e.g. those of Asian origin), should be monitored for adverse reactions potentially related to propylene glycol toxicity (i.e. seizures, stupor, tachycardia, hyperosmolarity, lactic acidosis, renal toxicity, haemolysis) (see section 4.3 Contraindications).

Kaletra is not a cure for HIV infection or AIDS. It does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Appropriate precautions should be taken. People taking Kaletra may still develop infections or other illnesses associated with HIV disease and AIDS.

There are limited data on salvage therapy on patients who have failed with Kaletra. There are ongoing studies to further establish the usefulness of potential salvage therapy regimens (e.g. amprenavir or saquinavir). There are currently limited data on the use of Kaletra in protease inhibitor-experienced patients.

Besides propylene glycol as described above, Kaletra oral solution contains ethanol (42 % w/w) which is potentially harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. It may modify or increase the effects of other medicines. Kaletra oral solution contains up to 0.8 g of fructose per dose when taken according to the dosage recommendations. This may be unsuitable in hereditary fructose intolerance. Kaletra oral solution contains up to 0.3 g of glycerol per dose. Only at high inadvertent doses, it can cause headache and gastrointestinal upset. Furthermore, polyoxol 40 hydrogenated castor oil and potassium present in Kaletra oral solution may cause only at high inadvertent doses gastrointestinal upset. Patients on a low potassium diet should be cautioned.

4.5 Interaction with other medicinal products and other forms of interaction

Kaletra contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A *in vitro*. Co-administration of Kaletra and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. Kaletra inhibits CYP2D6 *in vitro* but to a lesser extent than CYP3A. The clinical relevance of this inhibition has not been investigated. Kaletra does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations (see section 4.3 Contraindications).

Kaletra has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450 enzymes and by glucuronidation. This may result in lowered plasma concentrations and potential decrease of efficacy of co-administered medicinal products.

Medicinal products that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in section 4.3 Contraindications.

Antiretroviral agents

Nucleoside reverse transcriptase inhibitors (NRTIs):

Stavudine and Lamivudine: no change in the pharmacokinetics of lopinavir was observed when Kaletra was given alone or in combination with stavudine and lamivudine in clinical studies.

Didanosine: it is recommended that didanosine be administered on an empty stomach; therefore, didanosine is to be given one hour before or two hours after Kaletra (given with food). The gastroresistant formulation of didanosine should be administered at least two hours after a meal.

Zidovudine and Abacavir: Kaletra induces glucuronidation, therefore Kaletra has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Nevirapine: no change in the pharmacokinetics of lopinavir was apparent in healthy volunteers during nevirapine and Kaletra co-administration. Results from a study in HIV-positive paediatric patients revealed a decrease in lopinavir concentrations during nevirapine co-administration. The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric patients and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic interaction is unknown. No formal recommendation could be drawn on dosage adjustment when Kaletra is used in combination with nevirapine. However, based on clinical experience, Kaletra dose increase to 533/133 mg twice daily (~6.5 ml) may be considered when co-administered with nevirapine, particularly for patients in whom reduced lopinavir susceptibility is likely.

Efavirenz: when used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in multiple protease inhibitor-experienced patients, increasing the dose of Kaletra 33.3 % from 400/100 mg (3 capsules) twice daily to 533/133 mg (4 capsules) twice daily yielded similar lopinavir plasma concentrations as compared to historical data of Kaletra 400/100 mg (3 capsules) twice daily.

Dosage increase of Kaletra from 400/100 mg (5 ml) twice daily to 533/133 mg (~6.5 ml) twice daily should be considered when co-administered with efavirenz. Caution is warranted since this dosage adjustment might be insufficient in some patients.

Protease inhibitors (PIs):

Kaletra is expected to increase concentrations of the HIV protease inhibitors indinavir, nelfinavir and saquinavir. The pharmacokinetics of single-dose indinavir and saquinavir obtained in healthy volunteers after at least 10 days of Kaletra 400/100 mg twice daily were compared to historical data in HIV-infected patients. Because of limitations in the study design it is not possible to make definitive dosing recommendations. However, based on these comparisons, indinavir 600 mg twice daily and saquinavir 800 mg twice daily, when co-administered with Kaletra 400/100 mg twice daily, may produce a similar AUC and higher C_{min} relative to its respective established clinical dosing regimen. When co-administered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33 % and C_{min} increased 64 % as compared to Kaletra 400/100 mg (3 capsules) twice daily. Appropriate doses of HIV protease inhibitors in combination with Kaletra with respect to safety and efficacy have not been established.

Other medicinal products:

Antiarrhythmics (bepidil, systemic lidocaine and quinidine): concentrations may be increased when co-administered with Kaletra. Caution is warranted and therapeutic concentration monitoring is recommended when available.

Anticoagulants: Warfarin concentrations may be affected when co-administered with Kaletra. It is recommended that INR (international normalised ratio) be monitored.

Anticonvulsants (phenobarbital, phenytoin, carbamazepine): will induce CYP3A4 and may decrease lopinavir concentrations.

Dihydropyridine calcium channel blockers (e.g. felodipine, nifedipine, nicaldipine): may have their serum concentrations increased by Kaletra.

Disulfiram, metronidazole: Kaletra oral solution contains alcohol which can produce disulfiram-like reactions when co-administered with disulfiram or other medicinal products that produce this reaction.

HMG-CoA reductase inhibitors: HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with Kaletra. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicinal products with Kaletra is not recommended. Atorvastatin and cerivastatin are less dependent on CYP3A4 for metabolism. When atorvastatin was given concurrently with Kaletra, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with Kaletra, the lowest possible doses of atorvastatin and cerivastatin should be administered. Results from an interaction study with Kaletra and pravastatin reveal no clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with Kaletra. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Dexamethasone: may induce CYP3A4 and may decrease lopinavir concentrations.

Sildenafil: co-administration of sildenafil 100 mg single dose with ritonavir 500 mg twice daily at steady-state resulted in a 1000% increase in sildenafil plasma AUC. On the basis of these data, concomitant use of sildenafil with Kaletra is not recommended and in no case should the starting dose of sildenafil exceed 25 mg within 48 hours (see section 4.4 Special warnings and special precautions for use).

Cyclosporin and tacrolimus: concentrations may be increased when co-administered with Kaletra. More frequent therapeutic concentration monitoring is recommended until plasma levels of these products have been stabilised.

Ketoconazole and itraconazole: may have serum concentrations increased by Kaletra. High doses of ketoconazole and itraconazole (> 200 mg/day) are not recommended.

Clarithromycin: moderate increases in clarithromycin AUC are expected when co-administered with Kaletra. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered (see section 4.4 Special warnings and special precautions for use).

Methadone: Kaletra was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives: since levels of ethinyl oestradiol may be decreased alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives are co-administered.

Rifabutin: when rifabutin and Kaletra were co-administered for 10 days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or 3 times per week) is recommended when administered with Kaletra. Further reduction may be necessary.

Rifampicin: due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with Kaletra (see sections 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

St John's wort: patients on Kaletra should not use concomitantly products containing St John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of Kaletra. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see section 4.3 Contraindications).

Based on known metabolic profiles, clinically significant interactions are not expected between Kaletra and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin or fluconazole.

4.6 Pregnancy and lactation

There are no data from the use of Kaletra in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The potential risk for humans is unknown. Kaletra should not be used during pregnancy unless clearly necessary.

Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. HIV-infected women must not breast-feed their infants under any circumstances to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive a car and use machines have been performed.

Kaletra oral solution contains approximately 42 % w/w alcohol.

4.8 Undesirable effects

The safety of Kaletra has been investigated in 612 patients in Phase II/III clinical trials, of which 442 have received a dose of 400/100 mg (3 capsules) twice daily. In some studies, Kaletra was used in combination with efavirenz or nevirapine.

The most common adverse event associated with Kaletra therapy was diarrhoea occurring in approximately 14 % of patients and which was generally of mild to moderate severity. Discontinuation due to adverse reactions was 2.5 % (naïve patients) and 8 % (experienced patients) over a 24 week period.

It is important to note that cases of pancreatitis have been reported in patients receiving Kaletra, including those who developed hypertriglyceridaemia. Furthermore, rare increases in PR interval have been reported during Kaletra therapy (see section 4.4 Special warnings and special precautions for use: sections pancreatitis and lipids).

ADULT PATIENTS

Adverse events (≥ 2 % of patients):

The following adverse reactions of moderate to severe intensity with possible or probable relationship to Kaletra have been reported in ≥ 2 % of patients: diarrhoea 14 %, nausea 6 %, vomiting 2 %, abdominal pain 2.5 %, asthenia 4 % and headache 3 %.

Laboratory Abnormalities

Marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2 % of patients included: increased glucose (2.5 %), increased SGOT/AST (2 %), increased SGPT/ALT (2 %) increased GGT (9 %), increased total cholesterol (8.5 %) and increased triglycerides (8 %) (see section 4.4 Special warnings and special precautions for use: pancreatitis and lipids). For lipids elevations, each of these reactions is considered common.

Adverse events (1 – 2 % of patients):

Rash, abnormal stools, insomnia are considered common (occurrence 1 – 2 %).

Adverse events (< 1 % of patients) listed below by body system:

Haemic and Lymphatic System: anaemia, leucopenia, and lymphadenopathy.

Endocrine System: Cushing's syndrome and hypothyroidism.

Metabolic and Nutritional Disorders: avitaminosis, dehydration, oedema, decreased glucose tolerance, lactic acidosis, obesity, peripheral oedema, and weight loss.

Nervous System: abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, dyskinesia, emotional lability, encephalopathy, hypertonia, insomnia, decreased libido, nervousness, neuropathy, paresthesia, peripheral neuritis, somnolence, abnormal thinking, and tremor.

Special Senses: abnormal vision, eye disorder, otitis media, taste perversion, and tinnitus.

Cardiovascular System: hypertension, palpitation, thrombophlebitis, and vasculitis.

Respiratory System: bronchitis, dyspnea, lung oedema, and sinusitis.

Digestive System: abnormal stools, anorexia, cholecystitis, constipation, dry mouth, dyspepsia, dysphagia, enterocolitis, eructation, oesophagitis, faecal incontinence, flatulence, gastrointestinal disorder, gastritis, gastroenteritis, haemorrhagic colitis, increased appetite, pancreatitis (see section 4.4 Special warnings and special precautions for use: pancreatitis and lipids), sialadenitis, stomatitis, and ulcerative stomatitis.

Skin and Appendages: acne, alopecia, dry skin, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, skin benign neoplasm, skin discoloration and sweating.

Musculoskeletal System: arthralgia, arthrosis and myalgia.

Urogenital System: abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, and urine abnormality.

Others: back pain, chest pain, chest pain substernal, chills, cyst, face oedema, fever, flu syndrome and malaise.

PAEDIATRIC PATIENTS

In children 2 years of age and older, the nature of the safety profile is similar to that seen in adults. Rash (2 %) was the only drug-related clinical adverse event of moderate or severe intensity in ≥ 2 % of paediatric patients treated with combination therapy including Kaletra for up to 24 weeks. In 1 % of paediatric patients: allergic reaction, constipation, dry skin, fever, hepatomegaly, taste perversion and vomiting were reported.

Marked clinical laboratory abnormalities (Grade 3 or 4) reported in ≥ 2 % of paediatric patients included: high bilirubin (3 %), high SGPT/ALT (4 %), high SGOT/AST (7 %) high total cholesterol (2 %), high amylase (4 %), low sodium (3 %), low platelets (4 %) and low neutrophils (2 %). Each of these reactions is considered common.

Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

Combination antiretroviral therapy, including regimens containing a protease inhibitor, has been associated with redistribution of body fat in some patients. Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia. Clinical examination should

include evaluation for physical signs of fat redistribution. Consideration should be given to measurement of serum lipids and blood glucose. The mechanisms of these events and long term consequences, such as an increased risk of cardiovascular disease, are currently unknown (see section 4.4 Special warnings and special precautions for use).

4.9 Overdose

To date, there is limited human experience of acute overdose with Kaletra.

The adverse clinical signs observed in dogs included salivation, emesis and diarrhoea/abnormal stool. The signs of toxicity observed in mice, rats or dogs included decreased activity, ataxia, emaciation, dehydration and tremors.

There is no specific antidote for overdose with Kaletra. Treatment of overdose with Kaletra is to consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since Kaletra is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antiviral for systemic use, ATC code: J05A

Mechanism of action: Lopinavir provides the antiviral activity of Kaletra. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral activity *in vitro*: the *in vitro* antiviral activity of lopinavir against laboratory and clinical HIV strains was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean EC₅₀ of lopinavir against five different HIV-1 laboratory strains was 19 nM. In the absence and presence of 50 % human serum, the mean EC₅₀ of lopinavir against HIV-1_{IIIIB} in MT4 cells was 17 nM and 102 nM, respectively. In the absence of human serum, the mean EC₅₀ of lopinavir was 6.5 nM against several HIV-1 clinical isolates.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. HIV-1 has been passaged *in vitro* with lopinavir alone and with lopinavir plus ritonavir at concentration ratios representing the range of plasma concentration ratios observed during Kaletra therapy. Genotypic and phenotypic analysis of viruses selected in these passages suggest that the presence of ritonavir, at these concentration ratios, does not measurably influence the selection of lopinavir-resistant viruses. Overall, the *in vitro* characterisation of phenotypic cross-resistance between lopinavir and other protease inhibitors suggest that decreased susceptibility to lopinavir correlated closely with decreased susceptibility to ritonavir and indinavir, but did not correlate closely with decreased susceptibility to amprenavir, saquinavir, and nelfinavir.

Genotypic correlates of reduced phenotypic susceptibility to lopinavir in viruses selected by other protease inhibitors. The *in vitro* antiviral activity of lopinavir against 112 clinical isolates taken from patients failing therapy with one or more protease inhibitors was assessed. Within this panel, the following mutations in HIV protease were associated with reduced *in vitro* susceptibility to lopinavir: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V and L90M. The median EC₅₀ of lopinavir against isolates with 0 - 3, 4 - 5, 6 - 7 and 8 - 10 mutations at the above amino acid positions was 0.8, 2.7, 13.5 and 44.0-fold higher than the EC₅₀ against wild type HIV, respectively. The 16 viruses that displayed > 20-fold change in susceptibility all contained mutations at positions 10, 54, 63 plus 82 and/or 84. In addition, they contained a median of 3 mutations at amino acid positions 20, 24, 46, 53, 71 and 90.

Antiviral activity of Kaletra in patients failing protease inhibitor therapy. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to Kaletra therapy, with respect to baseline viral genotype and phenotype, in 56 patients previously failing therapy with multiple protease inhibitors. The EC₅₀ of lopinavir against the 56 baseline viral isolates ranged from 0.6 to 96-fold higher than the EC₅₀ against wild type HIV. After 24 weeks of treatment with Kaletra, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA \leq 400 copies/ml was observed in 93 % (27/29), 78 % (7/9), 67 % (4/6) and 50 % (4/8) patients with < 10-fold, 10 to 20-fold, 20 to 40-fold, and > 40-fold reduced susceptibility to lopinavir at baseline, respectively. In addition, virologic response was observed in 96 % (24/25), 76 % (16/21) and 33 % (2/6) patients with 0 - 5, 6 - 7, and 8 - 10 mutations of the above mutations in HIV protease associated with reduced *in vitro* susceptibility to lopinavir. Since these patients had not previously been exposed to either Kaletra or efavirenz, part of the response may be attributed to the antiviral activity of efavirenz, particularly in patients harbouring highly lopinavir resistant virus. The study did not contain a control arm of patients not receiving Kaletra.

Selection of viral resistance during Kaletra therapy. In Phase II studies of 227 antiretroviral treatment naïve and protease inhibitor experienced patients, isolates from four patients with quantifiable (> 400 copies/ml) viral load following treatment with Kaletra for \geq 12 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. The mean EC₅₀ of lopinavir against the four baseline isolates was 2.8-fold (range: 0.7 to 5.2-fold) higher than the EC₅₀ against wild type HIV, and each of the four baseline isolates contained four or more mutations in HIV protease associated with resistance to protease inhibitors. Following treatment of the four patients with Kaletra, the mean EC₅₀ of lopinavir increased to 55-fold (range: 9.4 to 99-fold) compared to wild type HIV, and 2 - 3 additional mutations at amino acids 10, 24, 33, 46, 54, 63, 71 and/or 82 were observed.

Cross-resistance: at this stage of development, little information is available on the cross-resistance of viruses selected during therapy with Kaletra. Isolates from 4 patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during Kaletra therapy either remained or developed cross-resistance to ritonavir, indinavir, and nelfinavir. All rebound viruses either remained fully sensitive or demonstrated modestly reduced susceptibility to amprenavir (up to 8.6-fold concurrent with 99-fold resistance to lopinavir). The rebound isolates from the two patients with no prior saquinavir treatment remained fully sensitive to saquinavir.

Clinical pharmacodynamic data

The effects of Kaletra (in combination with other antiretroviral agents) on biological markers (plasma HIV RNA levels and CD₄ counts) have been investigated in a controlled study of Kaletra of 24 weeks duration, and in additional studies of Kaletra of 72 weeks duration.

Adult Use

Patients without prior antiretroviral therapy

Study M98-863 is a randomised, double-blind trial of 653 antiretroviral treatment naïve patients investigating Kaletra (400/100 mg twice daily) compared to nelfinavir (750 mg three times daily) plus nucleoside reverse transcriptase inhibitors. By intent to treat analysis where patients with missing values are considered virologic failures, the proportion of patients at 24 weeks with HIV RNA < 400 copies/ml in the Kaletra arm was 79 % and 71 % in the nelfinavir arm. Mean baseline CD₄ cell count was 259 cells/mm³ (range: 2 to 949 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/ml (range: 2.6 to 6.8 log₁₀ copies/ml). Through 24 weeks of therapy, the proportion of patients in the Kaletra arm with plasma RNA < 50 copies/ml was 65 % and 60 % in the nelfinavir arm. The mean increase from baseline in CD₄ cell count was 154 cells/mm³ in the Kaletra arm and 150 cells/mm³ in the nelfinavir arm. Preliminary data at 48 weeks suggest that the virological response is sustained at long-term.

Sustained virological response to Kaletra (in combination with lamivudine and stavudine) has been also observed in a small Phase II study (M97-720) through 72 weeks of treatment.

Patients with prior antiretroviral therapy

Study M97-765 is a randomised, double-blind trial evaluating Kaletra at two dose levels (400/100 mg and 400/200 mg, both twice daily) plus nevirapine (200 mg twice daily) and two nucleoside reverse transcriptase inhibitors in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor naïve patients. Median baseline CD₄ cell count was 349 cells/mm³ (range 72 to 807 cells/mm³) and median baseline plasma HIV-1 RNA was 4.0 log₁₀ copies/ml (range 2.9 to 5.8 log₁₀ copies/ml). By intent to treat analysis where patients with missing values are considered virologic failures, the proportion of patients with HIV RNA < 400 (< 50) copies/ml at 24 weeks was 75 % (58 %) and the mean increase from baseline in CD₄ cell count was 174 cells/mm³ for the 36 patients receiving the 400/100 mg dose of Kaletra.

M98-957 is a randomised, open-label study evaluating Kaletra treatment at two dose levels (400/100 mg and 533/133 mg, both twice daily) plus efavirenz (600 mg once daily) and nucleoside reverse transcriptase inhibitors in 57 multiple protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor naïve patients. Median baseline CD₄ cell count was 220 cells/mm³ (range 13 to 1030 cells/mm³). By intent to treat analysis where patients with missing values are considered virologic failures, the proportion of patients with HIV RNA < 400 copies/ml at 24 weeks was 69 % and 82 % and the mean increase from baseline CD₄ cell count was 48 cells/mm³ and 41 cells/mm³ for patients receiving the 400/100 mg dose (n=29) and the 533/133 mg dose (n=28) of Kaletra, respectively.

Paediatric Use

M98-940 is an open-label study of a liquid formulation of Kaletra in 100 antiretroviral naïve (44 %) and experienced (56 %) paediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomised to either 230 mg lopinavir/57.5 mg ritonavir per m² or 300 mg lopinavir/75 mg ritonavir per m². Naïve patients also received nucleoside reverse transcriptase inhibitors. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors. Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after 3 weeks of therapy in each patient. Subsequently, all patients were continued on the 300/75 mg per m² dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14 patients less than 2 years old and 6 patients one year or less. Mean baseline CD₄ cell count was 838 cells/mm³ and mean

baseline plasma HIV-1 RNA was 4.7 log₁₀ copies/ml. Through 24 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/ml was 82 % for antiretroviral naïve patients and 66 % for antiretroviral experienced patients and the mean increase from baseline in CD₄ cell count was 328 cells/mm³ and 335 cells/mm³ respectively.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of Kaletra 400/100 mg twice daily yields mean steady-state lopinavir plasma concentrations 15 to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7 % of those obtained after the ritonavir dose of 600 mg twice daily. The *in vitro* antiviral EC₅₀ of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Absorption: multiple dosing with 400/100 mg Kaletra twice daily for 3 to 4 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption: Kaletra soft capsules and liquid have been shown to be bioequivalent under nonfasting conditions (moderate fat meal). Administration of a single 400/100 mg dose of Kaletra soft capsules with a moderate fat meal (500 – 682 kcal, 22.7 to 25.1 % from fat) was associated with a mean increase of 48 % and 23 % in lopinavir AUC and C_{max}, respectively, relative to fasting. For Kaletra oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 % and 54 %, respectively. Administration of Kaletra with a high fat meal (872 kcal, 55.8 % from fat) increased lopinavir AUC and C_{max} by 96 % and 43 %, respectively, for soft capsules, and 130 % and 56 %, respectively, for oral solution. To enhance bioavailability and minimise variability Kaletra is to be taken with food.

Distribution: at steady state, lopinavir is approximately 98 - 99 % bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg Kaletra twice daily, and is similar between healthy volunteers and HIV-positive patients.

Metabolism: *in vitro* experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir and therefore, increases plasma levels of lopinavir. A ¹⁴C-lopinavir study in humans showed that 89 % of the plasma radioactivity after a single 400/100 mg Kaletra dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but comprise only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the

induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 days to 2 weeks.

Elimination: after a 400/100 mg ¹⁴C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3 % and 82.6 ± 2.5 % of an administered dose of ¹⁴C-lopinavir can be accounted for in urine and faeces, respectively. Unchanged lopinavir accounted for approximately 2.2 % and 19.8 % of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3 % of the lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of lopinavir over a 12 hour dosing interval averaged 5 - 6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 l/h.

Special Populations

Paediatrics: there are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of Kaletra 300/75 mg/m² twice daily and 230/57.5 mg/m² twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 µg h/ml, 8.2 ± 2.9 µg/ml and 3.4 ± 2.1 µg/ml, respectively after Kaletra 230/57.5 mg/m² twice daily without nevirapine (n=12), and were 85.8 ± 36.9 µg h/ml, 10.0 ± 3.3 µg/ml and 3.6 ± 3.5 µg/ml, respectively after 300/75 mg/m² twice daily with nevirapine (n=12). The 230/57.5 mg/m² twice daily regimen without nevirapine and the 300/75 mg/m² twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine. Kaletra soft capsules and Kaletra oral solution are bioequivalent under nonfasting conditions.

Gender, Race and Age: Kaletra pharmacokinetics have not been studied in the elderly. No age or gender related pharmacokinetic differences have been observed in adult patients. Pharmacokinetic differences due to race have not been identified.

Renal Insufficiency: Kaletra pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency: Kaletra is principally metabolised and eliminated by the liver. Kaletra has not been studied in patients with hepatic insufficiency (see sections 4.3 Contraindications and 4.4 Special warnings and special precautions for use).

5.3 Preclinical safety data

Repeat-dose toxicity studies in rodents and dogs identified major target organs as the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration. While exposure eliciting these changes were comparable to or below human clinical exposure, dosages in animals were over 6-fold the recommended clinical dose. Mild renal tubular degeneration was confined to mice exposed with at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not other species. Serum cholesterol was elevated in rodents but not dogs, while triglycerides were elevated only in mice.

In dogs, prominent U waves on the electrocardiogram have been observed associated with prolonged PR interval and bradycardia. These effects have been assumed to be caused by electrolytic disturbance. However, these observations cannot rule out any potential cardiac effects of the medicinal product in humans (see also sections 4.4 Special warnings and special precautions for use, and 4.8 Undesirable effects).

In rats, embryofoetotoxicity (pregnancy loss, decreased foetal viability, decreased foetal body weights, increased frequency of skeletal variations) and postnatal developmental toxicity (decreased survival of pups) was observed at maternally toxic dosages. The systemic exposure to lopinavir/ritonavir at the maternal and developmental toxic dosages was lower than the intended therapeutic exposure in humans.

Long-term carcinogenicity studies of lopinavir/ritonavir in animal systems have not been completed. However, lopinavir/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, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Oral solution contains:

Alcohol (42 % w/w),
high fructose corn syrup,
propylene glycol,
purified water,
glycerol,
povidone,
Magnasweet-110 flavour (mixture of monoammonium glycyrrhizinate and glycerol),
vanilla flavour (containing p-hydroxybenzoic acid, p-hydroxybenzaldehyde, vanillic acid, vanillin, heliotrope, ethyl vanillin),
polyoxyl 40 hydrogenated castor oil,
cotton candy flavour (containing ethyl maltol, ethyl vanillin, acetoin, dihydrocoumarin, propylene glycol),
acesulfame potassium,
saccharin sodium,
sodium chloride,
peppermint oil,
sodium citrate,
citric acid,
menthol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store Kaletra oral solution at 2°C - 8°C (in a refrigerator). In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package. Avoid exposure to excessive heat.

6.5 Nature and content of container

Amber coloured multiple-dose polyethylene terephthalate (PET) bottles in a 60 ml size. Each pack contains 5 bottles of 60 ml (300 ml). The pack also contains 5 x 5 ml syringes with 0.1 ml graduations from 0 to 5 ml (400/100 mg).

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

EU/X/XX/XXX/XXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Abbott Laboratories, Queenborough, Kent ME11 5EL, United Kingdom

Manufacturing authorisation issued on 22 February 1999 by the Medicines Control Agency, Market Towers, 1 Nine Elms Lane, London, United Kingdom.

Abbott S.p.A 04010 Campoverde di Aprilia, Latina, Italy

Manufacturing authorisation issued on 14 May 1998 by the Ministero della Sanità, Viale della Civiltà Romana, 7, Roma, Italy.

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects

Follow up results of ongoing studies:

M98-863 (48 week report)	31 Mar 2001
M98-940 (48 week report)	30 Jun 2001
M98-957 (48 week report)	30 Jun 2001
M99-056 (48 week report)	31 Dec 2001
M98-888 (48 week report)	30 Jun 2002

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

BOX OF 2 BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Kaletra soft capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains: lopinavir 133.3 mg and ritonavir 33.3 mg (pharmacokinetic enhancer).

3. LIST OF EXCIPIENTS

Contains among others: propylene glycol, polyoxyl 35 castor oil, anhydriized liquid sorbitol (mixture of sorbitol, sorbitol anhydrides and mannitol), glycerol and sunset yellow (E110).

4. PHARMACEUTICAL FORM AND CONTENTS

180 soft capsules (2 bottles of 90 capsules each)

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use

Read the enclosed leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

Exp: {month/year}

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Kaletra soft capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains: lopinavir 133.3 mg and ritonavir 33.3 mg (pharmacokinetic enhancer).

3. LIST OF EXCIPIENTS

Contains among others: propylene glycol, polyoxyl 35 castor oil, anhydriized liquid sorbitol (mixture of sorbitol, sorbitol anhydrides and mannitol), glycerol and sunset yellow (E110).

4. PHARMACEUTICAL FORM AND CONTENTS

90 soft capsules

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use

Read the enclosed leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

Exp: {month/year}

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PACK OF 180 (5 CARTONS OF 6 BLISTERS OF 6 CAPSULES)

1. NAME OF THE MEDICINAL PRODUCT

Kaletra soft capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains: lopinavir 133.3 mg and ritonavir 33.3 mg (pharmacokinetic enhancer).

3. LIST OF EXCIPIENTS

Contains among others: propylene glycol, polyoxyl 35 castor oil, anhydriized liquid sorbitol (mixture of sorbitol, sorbitol anhydrides and mannitol), glycerol and sunset yellow (E110).

4. PHARMACEUTICAL FORM AND CONTENTS

Contains: 180 soft capsules (5 cartons of 6 foil blisters of 6 capsules).

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use

Read the enclosed leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp: {month/year}

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON OF 36 CAPSULES (6 BLISTERS OF 6 CAPSULES)

1. NAME OF THE MEDICINAL PRODUCT

Kaletra soft capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains: lopinavir 133.3 mg and ritonavir 33.3 mg (pharmacokinetic enhancer).

3. LIST OF EXCIPIENTS

Contains among others: propylene glycol, polyoxyl 35 castor oil, anhydriized liquid sorbitol (mixture of sorbitol, sorbitol anhydrides and mannitol), glycerol and sunset yellow (E110).

4. PHARMACEUTICAL FORM AND CONTENTS

Contains: 36 soft capsules (6 foil blisters of 6 capsules).

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use

Read the enclosed leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp: {month/year}

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 6 CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Kaletra soft capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited

3. EXPIRY DATE

Exp: {month/year}

4. BATCH NUMBER

Lot: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

300 ml of solution (5 bottles of 60 ml each)

1. NAME OF THE MEDICINAL PRODUCT

Kaletra oral solution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains: lopinavir 80 mg and ritonavir 20 mg (pharmacokinetic enhancer).

3. LIST OF EXCIPIENTS

Contains among others: alcohol (42 % w/w see leaflet), high fructose corn syrup, propylene glycol, glycerol, polyoxyl 40 hydrogenated castor oil, potassium (as acesulfame potassium).

4. PHARMACEUTICAL FORM AND CONTENTS

300 ml of solution (5 bottles of 60 ml each).

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use

Read the enclosed leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

Exp: {month/year}

9. SPECIAL STORAGE CONDITIONS

Store Kaletra oral solution at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot: {number]

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Kaletra oral solution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains lopinavir 80 mg and ritonavir 20 mg (pharmacokinetic enhancer).

3. LIST OF EXCIPIENTS

Contains among others: alcohol (42 % w/w see leaflet), high fructose corn syrup, propylene glycol, glycerol, polyoxyl 40 hydrogenated castor oil, potassium (as acesulfame potassium).

4. PHARMACEUTICAL FORM AND CONTENTS

60 ml of solution.

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Oral use

Read the enclosed leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Child resistant closure.

8. EXPIRY DATE

Exp: {month/year}

9. SPECIAL STORAGE CONDITIONS

Store Kaletra oral solution at 2°C - 8°C (in a refrigerator).

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist
- This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Kaletra is and what it is used for
2. Before you take Kaletra
3. How to take Kaletra
4. Possible side effects
5. Storing Kaletra
6. Further information

Kaletra soft capsules

- The active substance is lopinavir, the capsules also contain ritonavir which acts to increase the blood levels of lopinavir by inhibiting enzymes which metabolise it. Each capsule of Kaletra contains 133.3 mg of lopinavir and 33.3 mg of ritonavir (pharmacokinetic enhancer).
- The other ingredients are: oleic acid, propylene glycol, polyoxyl 35 castor oil, purified water.
- The capsule shell components are: gelatine, anhydriized liquid sorbitol (mixture of sorbitol, sorbitol anhydrides and mannitol), glycerol, titanium dioxide (white colour), sunset yellow (E110), medium-chain triglycerides, lecithin and black ink containing: propylene glycol, black iron oxide, polyvinyl acetate phthalate, polyethylene glycol 400 and ammonium hydroxide.

The marketing authorisation holder and the manufacturer of Kaletra is:

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

1. WHAT KALETRA IS AND WHAT IT IS USED FOR

How Kaletra is supplied

Kaletra soft capsules come in a plastic bottle containing 90 capsules. The capsules are orange with a black ink imprint of the [Abbott logo] and “PK”. Each capsule contains 133.3 mg of lopinavir and 33.3 mg of ritonavir. Two bottles of 90 capsules are provided in one package.

Kaletra soft capsules are also supplied in blisters. Each carton contains 6 foil blisters of 6 capsules (36 capsules). Each pack contains 5 cartons (180 capsules).

Kaletra is also supplied as an oral solution.

What Kaletra is

Kaletra 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 multiply.

When Kaletra should be used

Kaletra is used by adults and children 2 years of age or older who are infected with HIV, the virus which causes AIDS. Your doctor has prescribed Kaletra to help control your HIV infection. Kaletra does this by slowing down the spread of the infection in your body.

Kaletra is prescribed for use in combination with other antiviral medicines. Your doctor will determine which medicines are best for you.

2. BEFORE YOU TAKE KALETRA

Do not take Kaletra:

- if you are allergic to lopinavir, ritonavir or to any of the other ingredients.
- if you have severe liver problems
- if you are currently taking any of the following medicines:
 - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription).
 - midazolam, triazolam (used to relieve anxiety and/or trouble sleeping)
 - pimozide (used to treat schizophrenia)
 - cisapride (used to relieve certain stomach problems)
 - ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
 - rifampicin (used to treat tuberculosis)
 - amiodarone (used to treat abnormal heart beat)
 - flecainide and propafenone (heart medicines)

Patients taking Kaletra must not take products containing St John's wort (*Hypericum perforatum*) as this may result in the loss of therapeutic effect and development of resistance.

If you are currently taking any of these medicines, ask your doctor about switching to another medicine while you are taking Kaletra.

Take special care with Kaletra:

- Kaletra may interact with certain other medications with possible clinical effects. The use of the following medicines together with Kaletra should only take place on the basis of medical advice:
 - sildenafil, medicines used to lower blood cholesterol (e.g. lovastatin or simvastatin), some medicines affecting the immune system (e.g. cyclosporin, tacrolimus), several steroids (e.g. dexamethasone, ethinyl oestradiol), other protease inhibitors, certain heart medicines such as: calcium channel antagonists (e.g. felodipine, nifedipine, nicardipine) and medicines used to correct heart rhythm (e.g. bepridil, systemic lidocaine, quinidine), antifungals (e.g. ketoconazole, itraconazole), morphine-like medicines (e.g. methadone), anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital), warfarin, certain antibiotics (i.e. rifabutin, clarithromycin).
- taking certain medicines with Kaletra may result in increased levels in the body of these other medicines and could increase or prolong their effect and/or adverse reactions. You must tell your doctor about all the medicines, including those medicines you can buy

without a prescription, you are taking or are planning to take before you take Kaletra. This is because taking Kaletra with some medicines can result in serious or life threatening problems.

- if you are taking an oral contraceptive to prevent pregnancy, you should use an additional or different type of contraception since Kaletra may reduce the effectiveness of oral contraceptives.
- if you have liver disease or hepatitis. People with liver disease or hepatitis who take Kaletra may need additional testing. Your doctor will decide if this is needed for you.
- pregnant or nursing mothers should not take Kaletra unless specifically directed by their doctor (see also 'Pregnancy and breastfeeding').
- Kaletra should not be administered to children younger than 2 years of age unless specifically directed by their doctor.
- Kaletra is not a cure for HIV infection or AIDS. People taking Kaletra may still develop infections or other illnesses associated with HIV disease and AIDS. It is therefore important that you remain under the supervision of your doctor while taking Kaletra. Kaletra does not reduce the risk of passing HIV to others through sexual contact or blood contamination. You should use appropriate precautions.

Taking Kaletra with food and drink:

It is important that Kaletra is taken with food.

Pregnancy and breast-feeding:

Pregnant or breast-feeding mothers should not take Kaletra unless specifically directed by the doctor. Be sure to tell you doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility your baby can be infected with HIV through your breast milk.

Driving or using machines:

Kaletra has not specifically been tested for its possible affects on the ability to drive a car or operate machines.

Important information about some of the ingredients of Kaletra:

Sunset yellow [E110], a component of Kaletra soft capsules, can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

Taking other medicines:

Kaletra may interact with other medicines, including those you take without a prescription. It is possible that your doctor may increase or decrease the dose of other medicines when you are also taking Kaletra. You should tell your doctor about any medicines, including those medicines you can buy without a prescription, you are taking, or planning to take, before you take Kaletra. See Section 2, BEFORE YOU TAKE KALETRA, for further information.

If you are taking didanosine, it should be taken one hour before or at least two hours after taking Kaletra (with food). The gastroresistant formulation of didanosine should be administered at least two hours after a meal.

If you are taking sildenafil with Kaletra talk to your doctor about possible interactions with other medicines and side effects. If you take sildenafil and Kaletra together, you may be at risk of side effects such as low blood pressure, passing out, visual changes and penile erection lasting more than 4 hours. If an erection last longer than 4 hours, you should get medical help immediately to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

If you are taking an oral contraceptive to prevent pregnancy, you should use an additional or different type of contraception since Kaletra may reduce the effectiveness of oral contraceptives.

You should not take any medicines which you obtain without a prescription i.e. over-the-counter, or medicine-like products without consulting your doctor. Inform any doctor who prescribes medicine for you that you are taking Kaletra.

3. HOW TO TAKE KALETRA

It is important that you take Kaletra every day exactly as your doctor prescribed it. Even if you feel better, do not stop taking Kaletra without talking to your doctor. Using Kaletra as recommended should give you the best chance to delay the development of resistance to the product.

How and when should Kaletra be taken?

Always take Kaletra exactly the way your doctor has told you. The usual adult dose is 3 capsules twice a day i.e. every 12 hours, in combination with other anti-HIV medicines. For children, your doctor will decide the right dose based on the child's height and weight. It is important that all doses of Kaletra are taken with food.

Do not alter or discontinue the daily dose of Kaletra without first consulting with your doctor.

Kaletra should be taken twice every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking Kaletra as directed tell your doctor right away. Always keep enough Kaletra on hand so you don't run out. When you travel or need to stay in the hospital make sure you will have enough Kaletra to last until you can get a new supply.

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

If you take more Kaletra than you should:

If you realise you have taken more Kaletra than you were supposed to, contact your doctor right away. If you cannot reach your doctor, go to the hospital.

If you forget to take Kaletra:

It is important to take the total daily dose prescribed to ensure you get maximum benefit. If you miss a dose, take the missed dose as soon as possible together with some food, and then continue as before. However, if a dose is skipped, do not double the next dose. Continue on with your normal dose on the regular schedule as prescribed by your doctor.

4. POSSIBLE SIDE EFFECTS

What side effects might I have with Kaletra?

Like all medicines, Kaletra can have side effects. It may be difficult to differentiate between side effects caused by Kaletra and those which may arise due to other medicines you take at the same time or by the complications of the HIV infection. It is important that you inform your doctor of any change in your health.

The most common side effects of Kaletra are abdominal pain, abnormal stools and diarrhoea, feeling weak or tired, headache, nausea and vomiting.

In some individuals, treatment with protease inhibitors may cause changes in body shape due to changes in fat distribution. These may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck. Protease inhibitors may also cause hyperlipaemia (increase fats in the blood) and raised blood sugar.

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. Cases of diabetes mellitus or increased blood sugars have been reported in patients receiving Kaletra.

Some patients have had increases in the amount of triglycerides and cholesterol in the blood. There are no short-term risks that result from the increases observed. The long-term risks for complication such as heart attacks or stroke due to increases in triglycerides and cholesterol are not known at this time. Your doctor will monitor you and may prescribe other medicines if needed. In addition, large increases in the amount of triglycerides have also been considered a risk factor for pancreatitis. Pancreatitis should be considered if you experience clinical symptoms (nausea, vomiting, abdominal pain) which may be suggestive of this condition. If you experience these symptoms, tell your doctor.

Abnormal liver function tests have been reported in patients taking Kaletra. Some people had other illnesses or were taking other medicines. People with pre-existing liver disease or hepatitis may have worsening of liver disease.

There have been reports of muscle pain, tenderness or weakness, particularly in combination with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

Other uncommon side effects may occur with Kaletra. Ask your doctor or pharmacist for more information about side effects. Inform your doctor promptly about these or any other symptoms. If the condition persists or worsens, seek medical attention.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING KALETRA

As with all medicines, keep Kaletra out of the reach and sight of children.

How should I store Kaletra and for how long?

Kaletra soft capsules should be stored at 2°C - 8°C in a refrigerator. In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package. Avoid exposure to excessive heat.

It is important to keep Kaletra in the original package. Do not transfer it to any other container.

Do not use after the expiry date stated on the pack.

Further Information

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

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Tel: + 44 (0) 1628 773355

This leaflet was last approved on: *****

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist
- This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Kaletra is and what it is used for
2. Before you take Kaletra
3. How to take Kaletra
4. Possible side effects
5. Storing Kaletra
6. Further information

Kaletra oral solution

- The active substance is lopinavir, the oral solution also contains ritonavir which acts to increase the blood levels of lopinavir by inhibiting enzymes which metabolise it. Each ml of Kaletra contains 80 mg of lopinavir and 20 mg of ritonavir (pharmacokinetic enhancer).
- The other ingredients are: alcohol, high fructose corn syrup, propylene glycol, purified water, glycerol, povidone, Magnasweet-110 flavour (mixture of monoammonium glycyrrhizinate and glycerol), vanilla flavour (containing p-hydroxybenzoic acid, p-hydroxybenzaldehyde, vanillic acid, vanillin, heliotrope, ethyl vanillin), polyoxyl 40 hydrogenated castor oil, cotton candy flavour (containing ethyl maltol, ethyl vanillin, acetoin, dihydrocoumarin, propylene glycol), acesulfame potassium, saccharin sodium, sodium chloride, peppermint oil, sodium citrate, citric acid, menthol.

The marketing authorisation holder and the manufacturer of Kaletra is:

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL
United Kingdom

1. WHAT KALETRA IS AND WHAT IT IS USED FOR

How Kaletra is supplied

Kaletra oral solution comes in a multiple-dose 60 ml amber bottle. Five bottles of 60 ml are provided in one package. Each ml of Kaletra contains 80 mg of lopinavir and 20 mg of ritonavir.

Kaletra is also supplied as a capsule containing 133 mg of lopinavir and 33.3 mg of ritonavir.

What Kaletra is

Kaletra 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 multiply.

When Kaletra should be used

Kaletra is used by adults and children 2 years of age or older who are infected with HIV, the virus which causes AIDS. Your doctor has prescribed Kaletra to help control your HIV infection. Kaletra does this by slowing down the spread of the infection in your body.

Kaletra is prescribed for use in combination with other antiviral medicines. Your doctor will determine which medicines are best for you.

2. BEFORE YOU TAKE KALETRA

Do not take Kaletra:

- if you are allergic to lopinavir, ritonavir or to any of the other ingredients.
- If you have severe liver problems
- if you are currently taking any of the following medicines:
 - astemizole or terfenadine (commonly used to treat allergy symptoms – these medicines may be available without prescription).
 - midazolam, triazolam (used to relieve anxiety and/or trouble sleeping)
 - pimozide (used to treat schizophrenia).
 - cisapride (used to relieve certain stomach problems)
 - ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat headaches)
 - rifampicin (used to treat tuberculosis)
 - amiodarone (used to treat abnormal heart beat)
 - flecainide and propafenone (heart medicines)

Patients taking Kaletra must not take products containing St. John's wort (*Hypericum perforatum*) as this may result in the loss of therapeutic effect and development of resistance.

If you are currently taking any of these medicines, ask your doctor about switching to another medicine while you are taking Kaletra.

Take special care with Kaletra:

- Kaletra may interact with certain other medications with possible clinical effects. The use of the following medicines together with Kaletra should only take place on the basis of medical advice: sildenafil, medicines used to lower blood cholesterol (e.g. lovastatin or simvastatin), some medicines affecting the immune system (e.g. cyclosporin, tacrolimus), various steroids (e.g. dexamethasone, ethinyl oestradiol), other protease inhibitors, certain heart medicines such as: calcium channel antagonists (e.g. felodipine, nifedipine, nicardipine) and medicines used to correct heart rhythm (e.g. , bepridil, systemic lidocaine, quinidine), antifungals (e.g. ketoconazole, itraconazole), morphine-like medicines (e.g. methadone), anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital), warfarin, disulfiram, certain antibiotics (i.e. rifabutin, clarithromycin).
- Taking certain medicines with Kaletra may result in increased levels in the body of these other medicines and could increase or prolong their effect and/or adverse reactions. You must tell your doctor about all the medicines, including those medicines you can buy without a prescription, you are taking or are planning to take before you take Kaletra.

This is because taking Kaletra with some medicines can result in serious or life threatening problems.

- If you are taking an oral contraceptive to prevent pregnancy, you should use an additional or different type of contraception since Kaletra may reduce the effectiveness of oral contraceptives.
- if you have liver disease or hepatitis. People with liver disease or hepatitis who take Kaletra may need additional testing. Your doctor will decide if this is needed for you.
- Pregnant or nursing mothers should not take Kaletra unless specifically directed by their doctor (see also 'Pregnancy and breastfeeding').
- Kaletra should not be administered to children younger than 2 years of age unless specifically directed by their doctor.
- Kaletra is not a cure for HIV infection or AIDS. People taking Kaletra may still develop infections or other illnesses associated with HIV disease and AIDS. It is therefore important that you remain under the supervision of your doctor while taking Kaletra. Kaletra does not reduce the risk of passing HIV to others through sexual contact or blood contamination. You should use appropriate precautions.

Taking Kaletra with food and drink:

It is important that Kaletra is taken with food.

Pregnancy and breast-feeding:

Pregnant or breast-feeding mothers should not take Kaletra unless specifically directed by the doctor. Be sure to tell your doctor immediately if you are or may be pregnant or if you are breast-feeding a baby. It is recommended that HIV-infected women should not breast-feed their infants because of the possibility your baby can be infected with HIV through your breast milk.

Driving or using machines:

Kaletra has not specifically been tested for its possible effects on the ability to drive a car or operate machines.

Kaletra contains 42 % w/w alcohol.

Important information about some of the ingredients of Kaletra:

Kaletra contains 42 % w/w alcohol. Each dose contains up to 1.7 g of alcohol. Potentially harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. May modify or increase the effect of other medicines.

This medicinal product contains up to 0.8 g of fructose per dose when taken according to the dosage recommendations. Unsuitable in hereditary fructose intolerance. Due to the possibility of undetected fructose intolerance, this medicinal product should only be given to babies and infants after consultation with a physician.

Kaletra contains glycerol which is harmful in high doses. Can cause headache and stomach upset and diarrhoea.

Kaletra contains polyoxyl 40 hydrogenated castor oil. This may cause nausea, vomiting, colic, severe purgation at high doses. It should not be given when intestinal obstruction is present.

Kaletra contains potassium as acesulfame potassium, which may be harmful to people on a low potassium diet. High potassium in the blood can cause stomach upset and diarrhoea.

Kaletra contains sodium as saccharin sodium, sodium chloride and sodium citrate, which may be harmful to people on a low sodium diet.

Taking other medicines:

Kaletra may interact with other medicines, including those you take without a prescription. It is possible that your doctor may increase or decrease the dose of other medicines when you are also taking Kaletra. You should tell your doctor about any medicines, including those medicines you can buy without a prescription, you are taking, or planning to take, before you take Kaletra. See Section 2, BEFORE YOU TAKE KALETRA, for further information.

If you are taking didanosine, it should be taken one hour before or at least two hours after taking Kaletra (with food). The gastroresistant formulation of didanosine should be administered at least two hours after a meal.

If you are taking sildenafil with Kaletra talk to your doctor about possible interactions with other medicines and side effects. If you take sildenafil and Kaletra together, you may be at risk of side effects such as low blood pressure, passing out, visual changes and penile erection lasting more than 4 hours. If an erection last longer than 4 hours, you should get medical help immediately to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

If you are taking an oral contraceptive to prevent pregnancy, you should use an additional or different type of contraception since Kaletra may reduce the effectiveness of oral contraceptives.

Kaletra oral solution contains 42 % alcohol. While taking Kaletra oral solution you should not take medicines that cause a reaction with alcohol such as disulfiram. Talk to your doctor if you have any concerns.

You should not take any medicines which you obtain without a prescription i.e. over-the-counter, or medicine-like products without consulting your doctor. Inform any doctor who prescribes medicine for you that you are taking Kaletra.

3. HOW TO TAKE KALETRA

It is important that you take Kaletra every day exactly as your doctor prescribed it. Even if you feel better, do not stop taking Kaletra without talking to your doctor. Using Kaletra as recommended should give you the best chance to delay the development of resistance to the product.

How and when should Kaletra be taken?

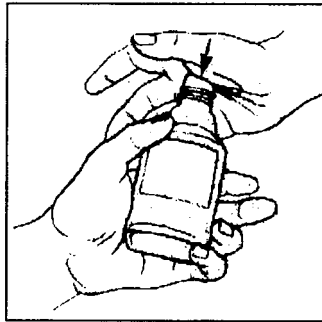
Always take Kaletra exactly the way you doctor has told you. The usual adult dose is 5 ml of the oral solution twice a day i.e. every 12 hours, in combination with other anti-HIV medicines. For children,

your doctor will decide the right dose based on the child's height and weight. It is important that all doses of Kaletra are taken with food.

Do not alter or discontinue the daily dose of Kaletra without first consulting with your doctor.

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 counter clockwise, or in the direction of the arrow. Talk to your pharmacist if you have difficulty opening the bottle.



5 dosing syringes are included in each carton of Kaletra oral solution. Ask your pharmacist for instructions on how to use the syringe correctly.

After each dose of Kaletra separate the plunger and the syringe. Wash the plunger and the syringe with dish soap and warm water as soon as you can; you may soak both in soapy water for up to 15 minutes. Rinse the syringe and plunger with clean water. Put the syringe back together and draw up and expel tap water a few times to rinse. Let the syringe dry completely before you use that syringe for dosing.

Kaletra should be taken twice every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking Kaletra as directed tell your doctor right away. Always keep enough Kaletra on hand so you don't run out. When you travel or need to stay in the hospital make sure you will have enough Kaletra to last until you can get a new supply.

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

If you take more Kaletra than you should:

If you realise you have taken more Kaletra than you were supposed to, contact your doctor right away. If you cannot reach your doctor, go to the hospital.

If you forget to take Kaletra:

It is important to take the total daily dose prescribed to ensure you get maximum benefit. If you miss a dose, take the missed dose as soon as possible together with some food, and then continue as before. However, if a dose is skipped, do not double the next dose. Continue on with your normal dose on the regular schedule as prescribed by your doctor.

4. POSSIBLE SIDE EFFECTS

What side effects might I have with Kaletra?

Like all medicines, Kaletra can have side effects. It may be difficult to differentiate between side effects caused by Kaletra and those which may arise due to other medicines you take at the same time or by the complications of the HIV infection. It is important that you inform your doctor of any change in your health.

The most common side effects of Kaletra are abdominal pain, abnormal stools and diarrhoea, feeling weak or tired, headache, nausea and vomiting.

In some individuals, treatment with protease inhibitors may cause changes in body shape due to changes in fat distribution. These may include decreased fat under the skin, increased fat in the abdomen (belly), breast enlargement and fatty lumps on the back of the neck. Protease inhibitors may also cause hyperlipaemia (increase fats in the blood) and raised blood sugar.

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. Cases of diabetes mellitus or increased blood sugars have been reported in patients receiving Kaletra.

Some patients have had increases in the amount of triglycerides and cholesterol in the blood. There are no short-term risks that result from the increases observed. The long-term risks for complication such as heart attacks or stroke due to increases in triglycerides and cholesterol are not known at this time. Your doctor will monitor you and may prescribe other medicines if needed. In addition, large increases in the amount of triglycerides have also been considered a risk factor for pancreatitis. Pancreatitis should be considered if you experience clinical symptoms (nausea, vomiting, abdominal pain) which may be suggestive of this condition. If you experience these symptoms, tell your doctor.

Abnormal liver function tests have been reported in patients taking Kaletra. Some people had other illnesses or were taking other medicines. People with pre-existing liver disease or hepatitis may have worsening of liver disease.

There have been reports of muscle pain, tenderness or weakness, particularly in combination with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis).

Other uncommon side effects may occur with Kaletra. Ask your doctor or pharmacist for more information about side effects. Inform your doctor promptly about these or any other symptoms. If the condition persists or worsens, seek medical attention.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING KALETRA

As with all medicines, keep Kaletra out of the reach and sight of children.

How should I store Kaletra and for how long?

Bottles of Kaletra oral solution should be stored at 2°C- 8°C in a refrigerator.

In use storage: If kept outside of the refrigerator, do not store above 25°C and discard any unused contents after 42 days (6 weeks). It is advised to write the date of removal from the refrigerator on the package.

Avoid exposure to excessive heat.

It is important to keep Kaletra in the bottle it came in. Do not transfer it to any other container.

Do not use after the expiry date stated on the bottle.

Further Information

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

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