persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a casual relationship between protease inhibitor therapy and these events has not been established.

Hepatic Impairment and Toxicity
Lopimune is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation.

Resistance/Cross-resistance
Various degrees of cross-resistance among protease inhibitors have been observed. The effect of **Lopimune** therapy on the efficacy of subsequently administered protease inhibitors is under investigation.

Hemophilia
There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia 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. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution
Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations
Treatment with **Lopimune** has resulted in large increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating **Lopimune** therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See Table 2 for additional information on potential drug interactions with **Lopimune** and HMG-CoA reductase inhibitors.

Side Effects
Treatment-emergent adverse events occurring in less than 2% of adult patients receiving **Lopimune** in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with **Lopimune** and of at least moderate intensity are listed below by body system.

Body as a Whole: Abdomen enlarged, allergic reaction, back pain, chest pain, chest pain substernal, cyst, drug interaction, drug level increased, face edema, fever, flu syndrome, hypertrophy, infection bacterial, malaise, and viral infection.

Cardiovascular System: Atrial fibrillation, deep vein thrombosis, hypertension, migrane, palpitation, thrombophlebitis, varicose vein and vasculitis.

Digestive System: Cholangitis, cholecystitis, constipation, dry mouth, dysphagia, entertis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, hemorrhagic colitis, increased appetite, jaundice, mouth ulceration, pancreatitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System: Cushing's syndrome, diabetes mellitus and hypothyroidism.

Hemic and Lymphatic System: Anemia, leukopenia and lymphadenopathy.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, weight gain and weight loss.

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

LOPIMUNE

Composition
Lopimune Capsules
Each soft gelatin capsule contains:
Lopinavir ..... 133.3 mg
Ritonavir ..... 33.3 mg

Lopimune Oral Solution
Each ml contains
Lopinavir ..... 80 mg
Ritonavir ..... 20 mg
Excipients ..... q.s.

Description
Lopimune (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in **Lopimune**, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Indications
Lopimune is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

Dosage and Administration
Adults
The recommended dosage of **Lopimune** is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

Concomitant therapy
Efavirenz or nevirapine: A dose increase of **Lopimune** to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).

Pediatric Patients
In children 6 months to 12 years of age, the recommended dosage of **Lopimune** oral solution is 12/3 mg/kg for those 7 to < 15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m²) twice daily taken with food, up to a maximum dose of 400/100 mg in children > 40 kg (5.0 mL or 3 capsules) twice daily. **It is preferred that the prescriber calculate the appropriate milligram dose for each individual child ≤ 12 years old and determine the corresponding volume of solution or number of capsules.** However, as an alternative, table 3 contains dosing guidelines for **Lopimune** oral solution based on body weight. When possible, dose should be administered using a calibrated dosing syringe.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of **Lopimune** oral solution to 13/3.25 mg/kg for those 7 to < 15 kg and 11/2.75 mg/kg for those 15 to 45 kg (approximately equivalent to 300/75 mg/m²) twice daily taken with food, up to a maximum dose of 533/133 mg in children > 45 kg twice daily is recommended when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Table 3 contains dosing guidelines for **Lopimune** oral solution based on body weight, when used in combination with efavirenz or nevirapine in children.

Table 1: Paediatric Dosing Guidelines

Weight (kg)	**Dose (mg/kg)***	**Volume of oral solution BID (80 mg lopinavir/ 20 mg ritonavir per mL)**
Without nevirapine or efavirenz		
7 to <15 kg	12 mg/kg BID	1.25 mL
7 to 10 kg		1.75 mL

lidocaine (systemic), and quinidine		tion monitoring is recommended for antiarrhythmics when co-administered with **Lopimune**, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, Phenobarbital, phenytoin	↓ Lopinavir	Use with caution, **Lopimune** may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Anti-infective: clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dose adjustments should be considered: • For patients with CL_{cr} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{cr} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: Ketoconazole, itraconazole	↑ Ketoconazole ↑ Itraconazole	High doses of ketoconazole or itraconazole (> 200 mg/ not recommended.
Antimycobacterial: rifabutin	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the dose of 300 mg/ day is recommended (i.e. a maximum 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction rifabutin may be necessary.
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone may be necessary.
Calcium Channel Blockers, Dihydropyridine: e.g. felodipine nifedipine, nicardipine	↑ Dihydropridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. **Lopimune** may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly
Neuroleptic Pimozide		**Contraindicated** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: Imidazolam, triazolam		**Contraindicated** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin		Potential for serious reactions such as risk of myopathy including rhabdomyolysis.

Other Drugs

Drug interaction studies reveal no clinically significant interaction between **Lopimune** and pravastatin, stavudine or lamivudine.

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

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

Particular caution should be used when prescribing sildenafil in patients receiving **Lopimune**. Co-administration of **Lopimune** with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, visual changes and sustained erection.

Concomitant use of **Lopimune** and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including **Lopimune**, with St. John's wort is expected to substatiallydecrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic respsone and possible resistance to lopinavir or to the class of protease inhibitors.

Pancreatitis

Pancreatitis has been observed in patients receiving **Lopimune** therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to **Lopimune** has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk of recurrence during **Lopimune** therapy.

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 **Lopimune** and/or other antiretroviral therapy should be suspended as clinically appropriate.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia

Lopimune is metabolized by CYP3A. Co-administration of Lopimune and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see Table 2). Although not noted with concurrent ketoconazole, co-administration of Lopimune and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with Lopimune are included in Table 3.

Table 2: Established and Other Potentially Significant Drug Interaction

Concomitant Drug Class: Drug Name Drug	Effect on Concentration of lopinavir or Concomitant	Clinical Comment
Non-nucleoside Reverse Transcriptase Inhibitors:efavirenz,	↓ Lopinavir	A dose increase of **Lopimune** to 533/133 mg (4 capsules nevirapine or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with **Lopimune**.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have notbeen established.
Nucleoside Reverse Transcriptase Inhibitor: Didanosine		It is recommended that It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after **Lopimune** (given with food).
HIV-Protease Inhibitors: Amprenavir, Indinavir, saquinaWr	When co-administered with reduced doses of concomitant protease inhibitors: ↑ Amprenavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Indinavir (Similar AUC, C_{max} ↑ C_{min}) ↑ Saquinalvr (Similar AUC; ↑ C_{max})	Alterations in concentrations (e.g., AUC, C_{max} and C_{min}) are noted when reduced doses of concomitant protease inhibitors are co-administered with **Lopimune**. Appropriate doses of the combination with respect to safety and efficacy have not been established.
HIV Protease Inhibitor: ritonavir	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with **Lopimune** with respect to safety and efficacy have not been established.
Antiarrhythmics: amiodarone,bepridil,	↑ Antiarrhythmics	Caution is warranted and therapeutic concentra
Disulfiram metronidazole		**Lopimune** oral solution contains alcohol, which can disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g. metronidazole).
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 hrs with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin,	↑ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with **Lopimune**.
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended in immunosuppressant agents when co-administered with **Lopimune**.
Narcotic Analgesic: Methadone	↓ Methadone	Dosage of methadone may need to be increased when co-administered with **Lopimune**.
Oral Contraceptive: ethinyl estradiol	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and **Lopimune** are co-administered.

Table 3: Drugs That Should Not Be Co-administered with Lopimune

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: flecainide, propafenone	**Contraindicated** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antihistamines: astemizole, terfenadine	**Contraindicated** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to **Lopimune** or to the class of protease inhibitors or other co-administered antiretroviral agents.
Ergot Derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**Contraindicated** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremeties and other tissues.
GI MotilityAgent: Cisapride	**Contraindicated** due to potential for serious and/orlife-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to **Lopimune** or to the class of protease inhibitors.

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

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

Respiratory System: Asthama, bronchitis, dyspnea, lung edema, pharyngitis, rhinitis and sinusitis.

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

Special senses: Abnormal vision, eye disorder, otitis media, taste perversion and tinnitus.

Urogenital system: Abnormal ejaculation, gynecomastia, hypogonadsm male, kidney calculus and urine abnormality.

Laboratory abnormalities
Adults
Increases in levels of glucose, uric acid, total bilirubin, SGOT/AST, SGPT,ALT, GGT, total cholesterol and triglycerides, Amylase were noted. Decreases in inorganic phosphorous, hematology and neutrophils were also observed.
Paediatrics
The adverse event profile seems similar to that for adult patients.
Rash (3%) was the only drug-related clinical adverse event of moderate or severe intensity in ≥ 2% of paediatric patients treated with combination therapy including lopinavir/ritonavir for upto 48 weeks in 100 pediatric patients between 6 to 12 years of age in **Study 940**.
High levels of sodium, total bilirubin, SGOT/AST, SGPT/ALT, total cholesterol and amylase were noted. Low levels of platelet count and neutrophils were also observed.

Overdosage
Lopimune oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with lopinavir/ritonavir is limited. Treatment of overdose with lopinavir/ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with lopinavir/ritonavir. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since **Lopimune** is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

Storage:
Store between 2°C- 8°C (in a refrigerator)

Presentation
Lopimune capsules — Container of 90s
Lopimune Oral Solution — Bottle of 100 ml

> 10 to <15 kg		
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
> 20 to 25 kg		2.75 mL
> 25 to 30 kg		3.5 mL
> 30 to 35 kg		4.0 mL
> 35 to 40 kg		4.75 mL
> 40 kg	Adult dose	5 mL (or 3 capsules)

*** Dosing based on lopinavir component of Lopimune solution (80 mg/20 mg per mL)**

Note: Use adult dosage recommendation for children > 12 years of age

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/ 20 mg ritonavir per mL)
With nevirapine or efavirenz		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1. 5 mL
> 10 to <15 kg		2.0 mL
15 to 45 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
> 20 to 25 kg		3.25 mL
> 25 to 30 kg		4.0 mL
> 30 to 35 kg		4.5 mL
> 35 to 40 kg		5.0 mL (or 3 capsules)
> 40 to 45 kg		5.75 mL
> 45 kg	Adult dose	6.5 mL (or 4 capsules)

*** Dosing based on lopinavir component of Lopimune solution (80 mg/20 mg per mL)**

Note: Use adult dosage recommendation for children > 12 years of age

Contraindications
Lopimune is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir. Co-administration of **Lopimune** is contraindicated with drugs that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Warnings and Precautions
ALERT: Find out about medicines that should NOT be taken with **Lopimune**.

Drug Interactions
Lopimune is an inhibitor of CYP3A (cytochome P450 3A) both *in vitro* and *in vivo*. Co-administration of **Lopimune** and drugs primarily metabolized by CYP3A (e.g. dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with **Lopimune**.

Lopimune inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with **Lopimune** at the recommended dose, but the magnitude is not known. **Lopimune** does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations. **Lopimune** has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

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