Abbott’s Commitment to Global HIV Care

Kaletra® (lopinavir/ritonavir) – also called Aluvia™ – is a co-formulated, boosted protease inhibitor that is an important treatment option in the fight against HIV. In August 2006, the World Health Organization (WHO) identified heat-stable lopinavir/ritonavir (LPV/r) tablets as the recommended protease inhibitor for second-line therapy in resource-limited settings, because it is co-formulated and does not require refrigeration, which are key benefits for patients living in the developing world.

This recognition signaled global acknowledgement of the role Abbott and LPV/r will play in helping to address the HIV epidemic in the developing world. As with the previous capsule formulation, Abbott has committed to register this medicine around the world. In addition, Abbott has made a substantial investment in new manufacturing capacity to meet the increasing demand for second-line therapy from the developing world for our new LPV/r tablet. In the 114 African, least developed, low- and lower middle-income countries (as defined by the World Bank and United Nations), we have filed in the nations where 90 percent of the developing world HIV population lives.

To help ensure that all patients who need our HIV medicine can get it, Abbott has implemented five practical measures:

- Innovation
- Broad Registration
- Lower-strength Tablet for Pediatric Use
- Building Ongoing and Quality Supply
- Tiered and Affordable Pricing.

1. Innovation

Abbott has been a leader in the global battle against HIV since the start of the epidemic. We have created diagnostic tools, pharmaceuticals and innovative philanthropic programs to combat the disease. Recently, Abbott developed Meltrex™, a technology that allows poorly soluble compounds to be bioavailable in a heat-stable tablet formulation. This innovation answers a critical unmet need in the developing world, where infrastructure and refrigeration are often limited or nonexistent.

Our lopinavir/ritonavir (LPV/r) tablet – known as Aluvia™ in most developing countries – is as effective as the Kaletra® soft-gel capsule. However, unlike the capsule, the tablet does not require refrigeration and patients take fewer pills, with or without food, as part of their treatment regimen.
Abbott has had a long-standing commitment to develop HIV medicines appropriate for pediatric use. Kaletra is indicated as the recommended second-line therapy in the World Health Organization (WHO) guidelines for the treatment of children living with HIV in the developing world. Kaletra oral solution is the only co-formulated protease inhibitor that is approved for the treatment of children with HIV.

Building on this commitment, Abbott has used its proprietary Meltrex technology to develop a lower-strength formulation of the LPV/r tablet. Global filings for this new product will begin by mid-2007. This will be of significant importance to children living with HIV, because this tablet, too, can be taken with or without food and does not require refrigeration.

Abbott will continue the development of a heat-stable ritonavir tablet. At the recent Conference on Retroviruses and Opportunistic Infections (CROI), we presented encouraging human bioavailability data on a variety of potential tablet formulations. While these data are promising, significant work is required to finalize this complex formulation.

2. Broad Registration

The original Kaletra® (lopinavir/ritonavir) capsule formulation is registered in 118 countries, making it the most widely registered HIV medicine (according to World Health Organization data). Currently, the new heat-stable tablet formulation has been filed or approved in 115 countries. Ultimately, this new tablet formulation will be registered even more broadly than the capsule, in more than 150 countries, keeping lopinavir/ritonavir the most widely available HIV medicine in the world.

Already, the Kaletra (or Aluvia™ in the developing world) tablet formulation has been filed or approved in those countries where more than 9 out of every 10 HIV patients live. The remaining filings will take place as quickly as the regulatory process and capacity of the relevant governments allow.

39.5 million people are living with HIV worldwide (UNAIDS). Abbott has filed or been approved for tablets in developed and developing countries where 90 percent of the world’s HIV population lives.
Current filing/approval status of Kaletra/Aluvia tablets

Updated as of April 2007  LPV/r Tablets
Filings 115
Approvals 76 of 115
The tablet has already been approved in 76 countries, including 12 in Africa, 12 in Latin America, and 20 in Asia. The remaining 32 countries represent nations in the United States, Canada and Europe. Abbott will continue to provide regular updates on our filing and regulatory progress.

The typical review time for new medicines in developing countries is 12 to 24 months, after the Certificate of Pharmaceutical Product (CPP) from the source country becomes available. CPPs for the lopinavir/ritonavir (LPV/r) tablets are in place and Abbott is working with regulatory agencies in developing countries to identify opportunities to accelerate regulatory review and approval timelines. In many cases, we have been able to accelerate the process. However, approval timing ultimately remains in the hands of the governments. Some developing countries also have limited regulatory processes and capacity in place, which slows progress.

Pending approval, Abbott is supplying HIV medicine in some countries on a humanitarian basis through other legal means, such as waiver processes, in conjunction with partner non-governmental organizations and governments.

3. Lower-strength Tablet for Pediatric Use

Prevention of mother-to-child transmission (PMTCT) has virtually eliminated the need for pediatric HIV treatment in developed countries. In developing countries, the situation could not be more different. According to UNAIDS, just 11 percent of HIV-positive pregnant women in need of antiretroviral medicine to prevent mother-to-child transmission of HIV in low- and middle-income countries are receiving them. Of the 530,000 children who were newly infected with HIV in 2006, the significant majority lived in sub-Saharan Africa. Only a quarter of adults who need HIV medicine receive it. For children, the situation is even worse. Almost nine out of every ten children go without.

Abbott’s Kaletra® (lopinavir/ritonavir) oral solution, which has been available since 2000, plays an important role in the battle against the pediatric HIV epidemic. It is the only co-formulated protease inhibitor therapy available for children in the developing world. Lopinavir/ritonavir (LPV/r) leads the World Health Organization (WHO) list of recommended second-line therapies for children.

Abbott has had a long-standing commitment to develop HIV medicines appropriate for pediatric use. Building upon the strengths of the oral solution, we have now developed a lower-strength tablet suitable for pediatric use. We are rapidly preparing to initiate the global registration process of this lower-strength formulation of the LPV/r tablet, which begins with European Medicines Agency (EMEA) and U.S. Food and Drug Administration (FDA) filings, by mid-2007. This new formulation will be of significant importance to children living with HIV. While the tablet should not be crushed, broken or chewed, it can be taken with or without food and does not require refrigeration. Abbott is the first company to develop a solid-formulated protease-inhibitor tablets specifically designed for children.
In an environment where few HIV formulations, especially protease inhibitors, exist that can be taken by pediatric patients, Abbott is one of the few companies to focus HIV development efforts on formulations suitable for pediatric use. It is part of our commitment to improve HIV treatment options for patients, especially in developing nations, where the burden for children is the greatest.

4. Building Ongoing and Quality Supply

Whether patients live in Soweto or Seattle, Brussels or Bangalore, they should have access to the same quality, proven medicine. In order to create and maintain supply of this quality medicine, Abbott committed significant resources to develop and make the tablet formulation of lopinavir/ritonavir. Kaletra® and Aluvia™ are produced on the same production line and are identical except for the tablet color and markings.

Once a patient is started on antiretroviral (ARV) therapy, it is critical that they continue treatment without interruption. Abbott has built state-of-the-art manufacturing facilities with the capacity to ensure production and consistent supply of our HIV medicines for all patients. These facilities have been fully inspected and approved by global regulatory authorities and are in compliance with current Good Manufacturing Practices (cGMP).
5. Tiered and Affordable Pricing

In 2002, Abbott made a commitment to HIV patients in Africa and least developed countries (LDCs) that we would sell our HIV medicines at $500 per patient per year. In 2006, Abbott announced that the Aluvia™ tablet, too, would cost $500 per patient per year in Africa and the LDCs. In these markets, Abbott’s HIV medicines cost about a third of what the lowest priced generics cost – where generics are available.

Some of the realities of the HIV/AIDS epidemic have changed since Abbott made the commitment in 2002. It became clear that concerns with affordability and access were not limited to Africa and LDCs. Therefore, we expanded our preferential pricing program to create a new tier for low- and lower middle-income countries, as defined by the World Bank, in August 2006. In April 2007, we announced a further reduction in the mid-tier price to $1,000 per patient per year in these countries. After these reductions in the price in low-and lower middle-income countries, Kaletra® and Aluvia are now the most affordable protease inhibitors, compared to other boosted or unboosted protease inhibitors that are recommended in the World Health Organization (WHO), U.S. Department of Health and Human Services (DHHS), the British HIV Association (BHIVA), and the International AIDS Society (IAS)-USA guidelines.

The Abbott preferential price is lower than any known generic lopinavir/ritonavir (LPV/r) price. In addition, no generic versions of Kaletra are WHO pre-qualified. No generic has entered any African or least developed country at or near $500 per patient per year in the past five years.

![Comparison with Abbott's Preferential Pricing Programs](chart.png)

These prices are the lowest reported examples in WHO Global Price Reporting Mechanism (www.who.int/hiv/amd/gprm). They do not reflect other sources. No generic versions of lopinavir/ritonavir are WHO pre-qualified.
Eligibility
Governments and programs fully funded by governments, U.N. systems organizations, non-governmental organizations (NGOs) and other not-for-profit institutional providers of HIV treatment in low- and lower middle-income countries are eligible for this preferential access program. In the low- and lower middle-income countries, Abbott will immediately begin discussions with individual countries where Abbott’s patents are respected to maximize the number of patients that can be provided Kaletra/Aluvia capsules and tablets at this new price. Learn more about access to and affordability of Abbott’s HIV medicines and the specific countries in Abbott’s preferential pricing program.
Indication and Important Safety Information About KALETRA

Indication

KALETRA® (lopinavir/ritonavir) is always used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV protease (PRO-tee-ase) inhibitor. KALETRA is for adults and for children age 6 months and older.

Once daily dosing of KALETRA in combination with other anti-HIV medicines is not recommended for people with previous HIV treatment and has not been evaluated in children (6 months to 12 years of age).

Important Safety Information

KALETRA does not cure HIV infection or AIDS and does not reduce the risk of passing HIV to others.

KALETRA should not be taken if you have had an allergic reaction to KALETRA or any of its ingredients, including lopinavir or ritonavir.

Taking KALETRA with certain drugs can cause serious problems or death. KALETRA should not be taken with dihydroergotamine, ergonovine, ergotamine, and methylergonovines such as Cafergot®, Migranal®, D.H.E. 45®, Ergotrate Maleate, and Methergine, as well as Halcion®, Hismanal®, Orap®, Propulsid®, Seldane®, or Versed®.

KALETRA should also not be taken with rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®; or with Flonase®, Mevacor®, Zocor®, or products containing St. John’s wort (Hypericum perforatum). Once daily KALETRA should not be taken with Agenerase®, Sustiva®, Viracept®, Viramune®, Dilantin®, Phenobarbital, or Tegretol®.

Particular caution should be used when taking Viagra®, Cialis®, or Levitra®, since the interaction with KALETRA may result in an increase in their related side effects. Discuss all medicines, including those without a prescription and herbal products you are taking or plan to take, with your doctor or pharmacist.

Pancreatitits and liver problems, which can be fatal, have been reported in patients receiving KALETRA. Tell your doctor if you have nausea, vomiting, or abdominal pain, which may be signs of pancreatitis, or if you have or have had liver disease such as hepatitis B or C.

In patients taking protease inhibitors, increased bleeding (in patients with hemophilia) and diabetes/high blood sugar have occurred.

Changes in body fat have been seen in some patients receiving antiretroviral therapy. The cause and long term health effects of these conditions are not known at this time. Some patients receiving KALETRA have had large increases in triglycerides and cholesterol.

Varying degrees of cross-resistance among protease inhibitors have been observed.

The most commonly reported side effects of moderate severity are: abdominal pain, abnormal bowel movements, diarrhea, feeling weak or tired, headache, and nausea. Children taking KALETRA may sometimes get a skin rash. This is not a complete list of reported side effects.
Diarrhea may be more common in patients taking Kaletra capsules once daily compared to the twice-daily dose (57% vs. 35% of mild to severe events and possibly related to the drug; and 16% vs. 5% of at least moderate severity and possibly related to the drug as found in a clinical study).

KALETRA oral solution contains alcohol.

Exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

KALETRA tablets should be stored at room temperature. Exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

Refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), KALETRA oral solution should be used within 2 months. Avoid exposure to excessive heat.

1 KALETRA Prescribing Information, October 2005