Kaletra des Laboratoires Abbott

Un antirétroviral clé inaccessible aux malades des pays pauvres

MSF
Campagne d'Accès aux Médicaments Essentiels

Documents publiés en mars 2006

- Lettre ouverte du 15 mars 2006 à Abbott, rédigée par MSF et signée par des médecins, des chercheurs et des organisations de lutte contre le sida (versions anglaise et française)
- Lettre de MSF pour commande du Kaletra, nouvelle formulation, à Abbott, et bon de commande correspondant (en anglais)
- Communiqué de presse de Médecins Sans Frontières, 15 mars 2006 (versions anglaise et française)
- Transcript (en anglais) de la téléconférence de presse organisée par MSF le 15 mars 2006
- Réponse de Abbott à MSF, datée du 17 mars 2006 (en anglais)
- Lettre ouverte de MSF à Abbott, 23 mars 2006 (versions anglaise et française)
- Document de briefing (en anglais): *"Abbott's new and improved Kaletra: only in the US... But what about the rest of the world"*
- Document de briefing (en anglais): *"Unnecessary delays by Abbott: the "CPP" myth debunked"*

Document en provenance du site internet de Médecins Sans Frontières
http://www.msf.fr/

Médecins Sans Frontières

Miles White
Chairman and CEO
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064

Paris, le 6 mars 2006

Monsieur,

Nous souhaitons vous faire part de notre vive inquiétude concernant l'absence de disponibilité dans les pays en développement de la nouvelle formulation lopinavir/ritonavir (LPV/r) issue de la technologie de melt-extrusion (meltrex) et commercialisé sous le nom de Kaletra (200/50mg), .

L'Organisation Mondiale de la Santé (OMS) a reconnu le LPV/r comme un médicament essentiel et va l'inclure dans ses nouvelles recommandations pour les traitements anti-rétroviraux de seconde ligne, pour lesquelles les inhibiteurs de protéase boostés constituent un élément clé.

Comme vous le savez, cette nouvelle formulation de LPV/r, approuvée par la l'US Food and Drug Administration en octobre 2005, constitue une avancée cruciale pour les patients des pays en développement par l'absence de restrictions alimentaires, une quantité moindre de comprimés à ingérer et surtout la possibilité de les conserver sans réfrigération. Les conditions de conservation de l'ancienne formulation entraînent un risque non négligeable d'utilisation de comprimés abîmés par des patients vivant dans des zones tropicales. Il est urgent que les pays en développement aient accès à cette nouvelle formulation thermostable de LPV/r. Aucun autre inhibiteur de protéase boosté n'est simple d'utilisation dans les climats chauds de la plupart de ces pays.

Nous demandons à Abbott de prendre les décisions suivantes afin de rendre accessible aux pays en développement ce médicament de seconde ligne indispensable :

1. **Enregistrer immédiatement cette nouvelle formulation de LPV/r, dans tous les pays où l'ancienne formulation est enregistrée ou en cours d'enregistrement, ainsi que dans tous les pays en développement.**

Selon la base de données AMDS de l'OMS portant sur l'enregistrement des produits, publiée en octobre 2005, l'ancienne formulation LPV/r (133/33.3 mg) est enregistrée dans 55 pays et en cours d'enregistrement dans 13 autres, ce qui couvre 68 des 69 pays éligibles du « Abbott's Access Program ». En revanche, la nouvelle formulation n'est enregistrée dans aucun autre pays que les Etats-Unis. Nous vous demandons d'entamer au plus vite une demande d'enregistrement de la nouvelle formule LPV/r (200/50mg) dans les pays en développement, afin de remplacer l'ancienne formulation par la nouvelle, comme cela a été fait aux Etats-Unis.

2. **Rendre public le nom des pays et les dates de demandes d'enregistrement pour cette nouvelle formulation, ainsi qu'un planning pour l'enregistrement dans les autres pays.**

Nous demandons qu'Abbott rende public le nom des pays et les dates auxquelles les dossiers d'enregistrement ont été déposés pour cette nouvelle formulation, afin que les acteurs de santé de ces pays puissent travailler avec les autorités nationales de régulation des médicaments pour éviter tout retard. Nous demandons également de fournir un planning pour les demandes d'enregistrements en cours.

3. **Publier le prix de cette nouvelle formulation de LPV/r pour les pays en développement et les pays à revenu intermédiaire.**

Depuis mai 2002, Abbott vend l'ancienne formule de LPV/r en Afrique et dans les pays en développement au prix de 500 $ par patient et par an sur une base « FOB » (le transport, l'assurance, les frais de dédouanement et les taxes étant à la charge de l'acheteur). Pour l'instant Abbott n'a pas rendu public le prix de la nouvelle formulation pour les pays en développement. Nous demandons à Abbott de fixer un prix qui soit au maximum du même montant que celui de l'ancienne formulation dans les pays les moins développés.

Le programme « Access » de Abbott pour l'ancienne formulation de LPV/r exclut les pays à revenus intermédiaires. Ainsi certains de ces pays paient ce produit 12 fois plus cher que les pays africains les moins développés. Nous vous demandons de rendre cette nouvelle formulation financièrement accessible pour les pays à revenus intermédiaires, dans lesquels des millions de personnes vivent avec moins de deux dollars US par jour.

4. **Développer une formulation thermostable de ritonavir (RTV) et la rendre accessible dans les pays en développement.**

Une formulation séparée et thermostable du ritonavir (RTV), commercialisé sous le nom de Norvir®, est également indispensable dans les pays en développement, afin que les soignants puissent appliquer les recommandations de l'OMS en associant le ritonavir avec d'autres inhibiteurs de protéase thermostables et accessibles financièrement.

5. **Développer une forme pédiatrique de cette nouvelle formulation de LPV/r.**

L'OMS recommande l'utilisation de LPV/r pour les enfants si une chaîne de froid efficace est accessible. Si la nouvelle formulation, thermostable, résout ce problème, elle ne permet pas pour autant une utilisation pédiatrique : le comprimé pelliculé, non sécable, est impossible à segmenter ou à écraser. Afin que les enfants, au même titre que les adultes, puissent avoir accès à un traitement efficace de seconde ligne, il est nécessaire de développer une formulation pédiatrique adaptée de LPV/r.

6. **Travailler avec les pays afin de rendre la nouvelle formulation de LPV/r accessible avant l'acceptation du dossier d'enregistrement.**

L'enregistrement d'un médicament peut prendre des mois, voire des années si le dossier n'est pas complet. Nous demandons à Abbott d'établir un système intérimaire fiable afin de rendre cette nouvelle formulation de LPV/r facilement accessible durant la période pendant le processus d'enregistrement.

Je vous prie d'agréer, Monsieur, l'expression de mes salutations distinguées.

March 15, 2006

Miles White
Chairman and CEO
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064

Dear Mr. White,

We are writing to you to express our concern about the lack of availability in developing countries of the new melt extrusion (Meltrex) formulation of lopinavir/ritonavir (LPV/r), marketed as Kaletra (200/50mg tablets).

LPV/r has been recognized as an essential medicine by the WHO[1] and will be included in its revised antiretroviral treatment guidelines[2], in which boosted protease inhibitors represent the cornerstone of second-line therapy. As you know, the tablet formulation of LPV/r, approved by the US Food and Drug Administration in October 2005, has critically important advantages for patients in developing countries: no dietary restrictions, lower pill burden, and most importantly, storage without refrigeration. Due to the storage requirements of the old formulation, there is the risk that some patients in tropical climates are currently using degraded LPV/r capsules. In short, there is an urgent need in developing countries for access to the new heat-stable formulation of LPV/r, as no other boosted protease inhibitors are practical to use in the hot climates of many of these countries.

We urge Abbott to take the following actions to make this crucial second-line option accessible in developing countries:

1. **Immediately file for registration of the new LPV/r formulation in all countries where the old formulation was registered or pending, as well as in other developing countries.**

According to the WHO/AMDS registration database[3] published in October 2005, the old formulation of LPV/r (133/33.3 mg soft gel capsules) is registered in 55 countries and registration is pending in 13 others, covering 68 of the 69 countries eligible in Abbott's Access Program.[4] But the new formulation of the drug has not been registered in any country except for the US. We urge you to immediately file for registration of the new formulation of LPV/r (200/50mg tablets) in developing countries, so that the old formulation can be replaced by the new one, as was done in the US.

2. **Communicate the countries and the filing dates where registration of the new formulation of LPV/r is pending and a timeline for submissions to remaining countries.**

We ask that Abbott communicate the countries and the filing dates where registration of the new formulation of LPV/r is pending so that health advocates in these countries can work with national drug regulatory authorities to overcome any delays and provide a timeline for submitting remaining registration requests.

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[1] 14th edition, WHO Model List of Essential Medicines (revised March 2005)
[2] Complete guidelines for adults and adolescents are forthcoming. A preliminary summary is available for consultation at http://www.who.int/3by5/mediacentre/news51/en/
[3] http://ftp.who.int/htm/AMDS/drugsdatabase.pdf (LPV/r is not listed as registered or pending in Eritrea which is eligible for Abbott's Access Program)
[4] http://www.accesstohivcare.org/en/partners/countries.aspx

3. Publish a price for the new formulation of LPV/r for least-developed and middle-income countries.

Since May 2002, Abbott has been selling the old formulation of LPV/r in Africa and Least Developed Countries for $500 per patient per year on an FOB basis (freight, insurance, customs handling, taxes and duties paid by purchaser). Abbott has not yet made public any price for the new formulation of LPV/r in developing countries. We ask that Abbott establish a price that is at least as low as the price for the old formulation in least-developed countries.

Abbott's Access Program for the old formulation of LPV/r excludes middle-income countries, resulting in prices up to 12 times more than in least-developed African countries.[5] We urge you to make the new formulation available at an affordable price in middle-income countries where millions live on less than US $2 per day.

4. Develop a heat-stable formulation of RTV and make it accessible in developing countries.

A separate, heat-stable formulation of ritonavir (RTV), marketed as Norvir, is also needed in developing countries so that care-providers can implement the forthcoming WHO guidelines and pair RTV with other available and affordable, heat-stable protease-inhibitors.

5. Develop a pediatric formulation of the new formulation of LPV/r.

WHO draft pediatric guidelines recommend LPV/r for use in children if there is cold-chain access.[6] While this new formulation overcomes the storage challenges presented by the old formulation, care-providers would not be able to cut or crush tablets because the new LPV/r is a coated tablet. Therefore, care-providers need a pediatric version of this formulation so that they can provide adequate second-line regimens for children as well as adults.

6. Work with countries to make the new formulation of LPV/r easily available while registration applications are being considered.

Because the drug registration process can take months if not years to complete, we ask that Abbott establish a reliable interim system to distribute this new formulation to treatment programs in developing countries while registration is pending.

Sincerely,

Stephen Lewis, United Nations Secretary General's Special Envoy for HIV/AIDS in Africa
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[5] Doctors Without Borders/Médecins Sans Frontières Briefing Note, "Abbott's New and Improved Kaletra: Only in the US," February 2006
[6] http://www.who.int/hiv/pub/guidelines/PaedARTguideDRAFT_webreviewNOV05%20_2_.pdf

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Open Letter To Abbott Laboratories from Doctors Without Borders/Médecins Sans Frontières (MSF)

March 15, 2006

Miles White
Chairman and CEO
Abbott Laboratories
200 Abbott Park Rd.
Abbott Park, IL 60064-6189

Sent via facsimile 847-938-6277 and email to miles.white@abbott.com

Dear Mr. White,

I am writing to you to inform you of the order (Order Number 31556) placed today by Doctors Without Borders/Médecins Sans Frontières (MSF) for the new tablet form of lopinavir/ritonavir (LPV/r), marketed as Kaletra.

As you are well aware, the LPV/r tablet, approved by the US Food and Drug Administration in October 2005, has critical advantages for patients in developing countries, including: no dietary restrictions, lower pill burden, and no refrigeration requirement. In Abbott's letter to MSF dated March 13, 2006, Abbott discussed the demands outlined in the enclosed letter signed by prominent HIV/AIDS researchers, practitioners, treatment advocates and people living with HIV/AIDS. However, Abbott failed to provide responses that address the immediate needs of our patients, and thousands of others, to access this drug. Therefore, MSF is asking Abbott to take concrete actions to make the new LPV/r accessible by placing this initial order (see attached).

In 2005, of the nearly 60,000 patients on antiretroviral treatment in MSF's HIV/AIDS programs worldwide, approximately six percent of patients those on treatment for three years were on second-line regimens. In Khayelitsha, South Africa, in an MSF program that has access to viral load monitoring, 16% of patients needed a new drug combination after four years of treatment. These data underline the acute and growing need for access to second-line drugs. According to the new WHO guidelines, boosted protease inhibitors, such as LPV/r, represent the cornerstone of second-line therapy.

Access to the new heat-stable formulation of LPV/r is urgently needed for patients cared for by MSF and other people living with AIDS in developing countries, especially in hot climates where refrigeration is not readily available.

When we inquired about Abbott's plans to market new LPV/r on December 21, 2005, Abbott replied that it would wait for European approval before initiating registration in developing countries, with the exception of South Africa where registration was supposed to be filed January 2006. In Abbott's communication with MSF on March 13, 2006, Abbott did not provide a price or timeline for registering

the new LPV/r formulation in developing countries, continuing to state that European approval was a prerequisite to registration. However, a Certificate of Pharmaceutical Product (CPP), which is required by some developing countries, could be issued by the US FDA as the product is sold in the US and could be exported from the US. Therefore, there is no barrier to file for registration. We urge you to act.

As you know, today Abbott has only made the new formulation of LPV/r available in the US at the Average Wholesale Price of $9687 per patient per year. For use in developing countries, MSF is prepared to pay no more than Abbott's differential price for the softgel LPV/r formulation of $500 per patient per year for this essential medicine. We have consulted industry experts and understand that at commercial volumes, the melt-extrusion process that provides heat-stability is less expensive.

MSF asks Abbott to do the following:

- Fulfill MSF's order (Order Number 31556) at the price of no more than US$500 per year per patient within 30 days.
- Immediately begin the process of registering the new LPV/r formulation (200/50 mg tablets) in developing countries, both in eligible "Access" countries as well as in middle-income developing countries;
- Publish the lowest possible price for the new formulation of LPV/r in developing countries;
- Extend this low price to middle-income countries as other companies have done, so that patients and care-providers in these countries can access heat-stable LPV/r.

MSF's initial order is for the following quantities in the following projects:

MSF Projects	**Number of Bottles**
Yaounde, Douala, Cameroon	420
Guatemala City, Guatemala	182
Busia, Mathare, Homa Bay, Nairobi, Kenya	901
Chiradzulu, Malawi	1112
Lagos, Nigeria	1205
Thailand	140
Arua, Uganda	55
Lusikisiki, South Africa	487
Matabeleland North, Zimbabwe	260
TOTAL	**4762**

This order would allow MSF to provide the new LPV/r formulation to nearly 800 patients by the end of 2006. MSF will acquire the necessary authorizations to import an unregistered drug from the relevant authorities and has already begun this process in several of the countries listed above.

MSF requests that our order be delivered to MSF's procurement center (MSF Logistique), a bonded pharmaceutical warehouse in Bordeaux, France so that we can ensure timely delivery to our projects in the above listed countries. MSF Logistique has been in operation since 1986 and has been a pharmaceutical establishment for wholesale distribution for humanitarian organizations since 1999. In addition, MSF Logistique is used by WHO to procure and manage global stocks of trypanomiasis drugs.

MSF recognizes the new formulation of LPV/r is needed by many care-providers in developing countries, and we urge you to set up an easy-to-use, temporary, distribution channel, until registration is complete so that patients outside of MSF projects can also access the new formulation of LPV/r.

If Abbott will not supply MSF with this order, MSF will have to adjust its procurement plans to avoid leaving patients untreated, and so we ask that Abbott inform MSF of its decision to supply MSF with the new tablet formulation of LPV/r within 5 business days. Please contact me at 212-679-6800 with any questions regarding the terms of this order. I look forward to your response.

Sincerely,

Nicolas de Torrente
Executive Director
MSF-USA

encl: Copy of MSF order placed on March 15, 2006
Copy of letter dated March 15, 2006 from HIV/AIDS researchers, clinicians, treatment advocates

cc:
Heather Mason, Vice President, International Marketing, Abbott Laboratories
Robert Dintruff, Director, Global Cares Initiative, Abbott Laboratories
Rita Roy, Global Citizen Shop, Abbott Latoratories

M S F
Logistique

Medecins Sans Frontieres Logistiqu - *Non profit association*
14, Avenue de l'Argonne -33700 Mérignac - FRANCE
Code APE 913 E -Siret 339 349 771 000 32 -VAT FR 84 339 349 771 -Bank: BPSO
13 Avenue de la Libération Mérignac - 10907 0001 Iban FR76 1090 7000 0142
0211 0613 710 Swift(BIC): CCBPFRPPBDX - Tél. +33 (0) 5.56.13.73.73
Fax +33 (0) 5.56.13.73.74 - E-mail : office@bordeaux.msf.org

N° 31556 14-MAR-06
PURCHASE ORDER
ABUS
BDX

ORDER TO:

ABBOTT LABORATORIES
Dept. 06MQ
Building AP34-3
600646189Abbott Park
UNITED STATE +1.847.938.7945
+1.847.938.8497

DESTINATION OF GOODS :

MSF Logistique - Bordeaux
14, Avenue de l'Argonne

33700 MERIGNAC
FRANCE 05 56 13 73 73
05 56 13 73 74

YOUR REFERENCE: M. Robert Dintruff

OUR REFERENCE: DELOUCHE Bruno

Code n°	Description	Qté Unit.tot.		Qté Pack	Cond.Pack	Prix Pack.	Prix Total
kaletra	LOPINAVIR (LPV) 200 mg + RITONAVIR (r) 50 mg, tab.	571320	=	4761	X 120		

registration number in US : NDA 021906

COMM ACHAT

Dear Mr Dintruff
Please acknowlege receipt for this order and please confirm
Price and estimated delivery lead time.

READ CAREFULLY :
PLEASE MENTION OUR PO NUMBER ON YOUR INVOICE

****

PLEASE RETURN

RECEIPT ON : ESTIMATED DELIVERY DATE :

****

PURCHASING PROVISIONS:

PLEASE REFER TO OUR GENERAL PURCHASING PROVISIONS
IMPORTANT: PHARMACEUTICAL SUPPLIERS SHOULD PROVIDE CERTIFICATE OF ANALYSIS .

PAYMENT-TERMS BANK TRANSFER .

TOTAL 0.00 USD

COMMUNIQUÉ DE PRESSE

Sida : les nouveaux traitements clés inaccessibles aux malades des pays pauvres

MSF demande aux laboratoires Abbott de rendre disponible le nouveau Kaletra à un prix abordable dans les pays pauvres

Paris/Lagos/New York, le 15 mars 2006. Les malades du sida dans les pays en développement sont privés des innovations thérapeutiques qui pourraient leur sauver la vie. Nous refusons la pratique courante des sociétés pharmaceutiques, qui commercialisent en Afrique, en Asie et en Amérique Latine des médicaments inadaptés et réservent les innovations aux seuls pays capables de les payer au prix fort.

Aujourd'hui, MSF a commandé au siège des Laboratoires Abbott à Chicago la nouvelle version résistante à la chaleur de leur médicament lopinavir/ritonavir. L'ancienne version, commercialisée sous le nom de Kaletra depuis 2000, est une gélule devant être réfrigérée, à prendre en grandes quantités et avec un régime alimentaire particulier. La nouvelle, thermostable, n'est pour l'instant vendue qu'aux Etats-Unis, au prix de 9.687 dollars par an et par patient (moyenne du prix de gros).

« Ici, la température dépasse régulièrement les 40°C et les réfrigérateurs ne sont pas fiables à cause des coupures de courant quotidiennes. Impossible pour nos patients d'utiliser l'ancienne version de ce médicament », explique Helen Bygrave, du programme MSF à Lagos, au Nigéria. *« Quelle cruelle ironie qu'un médicament qui n'a pas besoin d'être conservé au frais, et semble donc conçu spécialement pour des pays comme le Nigéria, ne soit pas disponible ici ! »*

En novembre 2005, Abbott lançait aux États-Unis la nouvelle version de son inhibiteur de protéase, le lopinavir/ritonavir. À la différence de la version précédente, celle-ci ne nécessite aucune réfrigération et est donc bien mieux adaptée au climat chaud de nombreux pays où MSF travaille. Pourtant, lorsque MSF s'est enquis de la disponibilité et du prix de ce nouveau produit pour ses patients, Abbott a répondu qu'elle attendrait sa mise en vente en Europe avant de demander une autorisation de commercialisation pour les pays pauvres. Les personnes qui ont le plus besoin de ce nouveau médicament clé – recommandé par l'OMS pour les traitements antirétroviraux (ARV) de deuxième ligne – seraient ainsi condamnées à attendre plusieurs années avant d'y avoir accès.

À Khayelitsha, en Afrique du Sud, 16 % des patients soignés par MSF ont dû changer de traitement au bout de quatre ans lorsqu'ils ont développé des résistances aux premières molécules. Cela montre à quel point le besoin de nouveaux médicaments est vital, en constante augmentation. La vie des 60 000 patients sous ARV dans nos programmes est menacée par la mauvaise volonté des laboratoires pharmaceutiques à rendre disponibles leurs nouveaux médicaments dans les pays pauvres.

Ibrahim Umoru, soigné à la clinique de Lagos, prend l'ancienne version de lopinavir/ritonavir depuis cinq semaines. Mais ses médicaments doivent être conservés au froid, dans une clinique loin de chez lui. *« Je n'ai pas les moyens d'avoir un réfrigérateur. Or la chaleur fait fondre les capsules qui se collent les unes aux autres et ressemblent à du vieux chewing-gum. J'ai besoin de la nouvelle version. »*

MSF a commandé aujourd'hui cette nouvelle version pour 9 de ses projets (Cameroun, Guatemala, Kenya, Malawi, Nigéria, Afrique du Sud, Thaïlande, Ouganda et Zimbabwe). Des spécialistes confirmant que la nouvelle formule pharmaceutique coûte moins cher à produire que l'ancienne, MSF a exigé un prix inférieur ou égal à celui que paient actuellement certains pays en développement pour l'ancienne version.

Dans une lettre adressée au PDG d'Abbott, des médecins et des chercheurs renommés ont joint leur voix à celles d'organisations de lutte contre le sida pour demander à l'entreprise de mettre au plus vite à la disposition des patients de ces pays, la nouvelle version du Kaletra.

Cette confrontation illustre de manière criante la situation inquiétante à laquelle les pays pauvres sont confrontés en matière d'accès aux médicaments. Alors que les prix des antirétroviraux de première génération avaient considérablement baissé du fait de l'apparition des génériques, ceux des nouveaux médicaments, soumis au monopole résultant des brevets, connaissent une hausse vertigineuse. Ils excluent de fait les pays où vivent la très grande majorité des malades du sida. Si l'accès aux nouveaux traitements repose sur la seule politique commerciale des laboratoires pharmaceutiques, la survie de millions de malades sera hypothéquée.

PRESS RELEASE

Access Denied to Crucial New HIV/AIDS Medicines

Urgent need in the developing world for Abbott Laboratories' new version of lopinavir/ritonavir, a drug that does not require refrigeration

Lagos/Berlin/New York, March 15, 2006 — People living with HIV/AIDS in developing countries can't get new and/or improved drugs that can make a critical difference, said the medical humanitarian organization Doctors Without Borders/Médecins Sans Frontières (MSF). MSF also said that it refuses to accept the standard practice of drug companies to market less adapted drugs to African, Asian and Latin American countries while reserving improved or newly developed drugs for countries that can pay more. For this reason MSF is placing an order directly with the worldwide headquarters of Abbott Laboratories in Chicago for a new heat stable version of the drug called lopinavir/ritonavir, which the company right now only sells in the US at a price of US$9,687 (average wholesale price) per patient per year.

"With temperatures regularly rising to nearly 40 Celsius, over 100 Fahrenheit, and with the numerous daily electrical blackouts, our patients can't use the old version of this drug," said Dr. Helen Bygrave, who works at MSF's AIDS treatment program in Lagos, Nigeria. "It's a cruel irony that although this drug — with no need for refrigeration — seems to have been designed for places like Nigeria, it is not available here."

In November 2005, Abbott launched a new version of their boosted protease inhibitor, lopinavir/ritonavir in the US. Unlike the old version, this new one no longer requires refrigeration, making it much more suitable for use in the hot climates of many developing countries where MSF works. But when MSF inquired about the price and availability of this new product for its patients, Abbott responded that it would wait until the product was available in Europe before requesting marketing approval in developing countries. This means a potential delay of years before this drug reaches the people who can benefit from it most.

The drug lopinavir/ritonavir is a crucial component of antiretroviral therapy for patients that need to be switched to a newer 'second-line' treatment regimen when drug resistance naturally develops after a few years on their first set of medications. World Health Organization (WHO) experts recommend this drug for use in second-line AIDS treatment.

At MSF's program in Khayelitsha, South Africa, 16% of the patients needed a new regimen after four years of treatment. Such data underline the acute and growing need for newer drugs. With over 60,000 patients on antiretroviral treatment, MSF says that its efforts to treat some patients that need access to newer drugs are being thwarted by drug company policies that take a "go slow" approach to making these new drugs available in developing countries.

Ibrahim Umoru, who receives treatment at the MSF clinic Lagos, has been taking the old version of LPV/r for five weeks but his drugs need to be refrigerated at a clinic that is far from his home. "I can't afford the diesel fuel for a generator to run a refrigerator. And without a refrigerator, these temperatures turn the capsules into clumps that look like used chewing gum. I need the newer version."

Because Abbott is not making the drug available in developing countries, MSF today placed an order for its projects in Cameroon, Guatemala, Kenya, Malawi, Nigeria, South Africa, Thailand, Uganda, and Zimbabwe. Armed with evidence from industry experts that the new formulation is less expensive to make than the old one, they also demanded the lowest possible price, one that would be no more than the amount Abbott charges some developing countries for the old version.

In a letter to the CEO of Abbott, prominent doctors, researchers and AIDS organizations from around the world urged Abbott to make new lopinavir/ritonavir available "immediately" to patients in developing countries.

Abbott has been marketing this drug as Kaletra since 2000 — but the old version is a soft-gel capsule, which means more pills per day, meal restrictions, and need for refrigeration in hot climates.

The current crisis of access to lopinavir/ritonavir is a clear illustration that the drug access problem in developing countries is still acute. While the price of first generation ARV medicines has decreased considerably because of generic competition, the price of new life extending drugs which are likely to be patented in producing countries are dramatically higher than older drugs. This blocks access in poorer countries where most people suffering from AIDS reside. If drug access depends on the marketing policies of pharmaceutical companies, then the lives of millions of patients will remain threatened.

Doctors Without Borders/Médecins Sans Frontières (MSF)
Press Teleconference on Lopinavir/Ritonavir
March 15, 2006

Kate Evans, US Coordinator of MSF's Campaign for Access to Essential Medicines:

Thank you -- thank you to everybody for joining us today. I would just like to begin by welcoming everyone as we discuss the need for newer antiretroviral (ARV) medicines to treat HIV/AIDS in developing countries. And in particular, the need for Abbott Laboratories's new heat stable formulation of lopinavir/ritonavir which is marketed as Kaletra. Currently MSF provides ARV therapy to nearly 70,000 patients in 51 projects across 31 countries. And what is important to understand is that as patients spend more and more time on treatment, it is inevitable that they develop resistance to the HIV medicines they're taking. And so, like in the U.S. and Europe, our patients and thousands of others on treatment need access to newer drugs to continue to be able to fight HIV.

The new formulation of lopinavir/ritonavir by Abbott Laboratories does not require refrigeration which makes this a critical component of the second-line treatment regimens we use. And it makes it one of the very few options that we have that are actually adapted for use in developing countries. However, today this drug is only available in the U.S. Because MSF has an urgent need to provide this drug to our patients, we have placed an order today with Abbott's worldwide headquarters in Chicago to meet the needs of our patients.

To discuss this issue further we will be speaking with Nathan Ford, the Coordinator of MSF's Campaign for Access to Essential Medicines in South Africa. Dr. Jens Henkel, a clinician in an MSF HIV/AIDS treatment project in Lagos, Nigeria,, and Dr. Binta Biawardinai, the Medical Coordinator of MSF's projects in Homa Bay, Kenya. We will hear from each of our speakers for just a few minutes and then open it up to questions.

So at this point I'd like to turn it over to Nathan Ford.

Nathan Ford: Hi, thank you, Kate. Thank you to everyone for joining us.

I'm sitting in South Africa at the moment. I'm working in an HIV program where we have two sites treating patients. One is in the western cape near Cape Town where we treat three-and- a-half thousand patients. And the other in the eastern cape, in Lusikisiki, where we have another one-and-a-half thousand patients on treatment. We've been working here for about five years. And we've been seeing that the general trend is a need for second-line drugs after four years of treatment on first-line medicines. Today, around 16 percent of patients need second-line treatment. We can be pretty sure that that's going to get higher and higher as time goes on.

Here in Lusikisiki in the Eastern Cape it's around 37 degrees Celsius [99 degrees F]. It's a very, very hot day. Half the clinics have no electricity and certainly most of the people we're helping have no refrigerators. So this second line drug that we're pushing for today, the lopinavir/ritonavir combination that doesn't need to be refrigerated, seems to me to be designed for use in Africa, precisely in these sections where people don't have refrigeration or electricity. And it's very frustrating for me to consider that this drug might not be available in Africa for many, many years to come. So we think it's important that Abbott make clear commitments to making this drug registered and available and affordable as soon as possible.

Now it's not just MSF in South Africa that needs this drug. There have been clear demands from physicians all over South Africa and in fact from many other countries who have signed on to a letter to try and push Abbott to make these commitments. We have physicians from roughly 25 countries that have signed on to a letter demanding three things from Abbott. The first is that Abbott takes seriously the registration of this drug. One of the problems with accessing drugs is that they might be available on the general market, but unless the company actually takes steps to register the drug, the public sector cannot use those medicines and that can lead to several years' delay. We've seen it with

other medicines and we're very, very concerned that we're going to see that problem with this medicine. So they need to submit registration requests immediately so that the drug can be used in the public sector as soon as possible. Second, we want Abbott to work on finding interim solutions so they don't just file the dossier and then sit on their hands and we have to wait two years before the drug is registered. We need to make absolutely certain that strong interim measures are in place so that we can start using this drug as soon as possible. And then, finally, we need to make sure the drug is affordable. I understand that currently the market price for the drug in America is around nine-and-a-half thousand dollars. Now, that's a price that nobody in this country can afford and we need to make absolutely sure that the company is making firm guarantees to roll out this medicine at an affordable price.

As I say, it's a drug that we need right now in our programs in South Africa, but we're going to be needing it even more because as the number of patients on treatment mature — and more and more patients have been on treatment over time — then more and more of those patients will have to move from the older medicines to the newer medicines. So it's an acute need for us now, but it will be an even greater need as time goes on. We're taking this course of action today because we see an ever increasing problem.

Kate Evans: Thanks very much, Nathan. And now we'll hear from Dr. Jens Wenkel, who actually just came from a press conference in Lagos, Nigeria and is treating patients in our HIV/AIDS project there.

Dr. Jens Henkel: Hello. Thank you and welcome to everybody. Greetings from Lagos. I'm working here as a doctor in Lagos where right now we have 1,200 patients on ARV treatment. We have started them on the first-line regiment recommended by the World Health Organazation. The problem in our project is probably the same faced by many others right now and will face in the future: about 10 percent of our patients are in need of a second-line treatment because of therapy failure That means if they run into clinical failure and develop all kinds of infections, we don't have a really stable and efficient second-line treatment for them. So we feel responsible as an organization, and as well as physicians, to not to let the patients down and provide an effective second-line regiment.

Now the cornerstone drugs recommended from the World Health Organization (WHO) in second-line treatment are protease inhibitors (PI), like the lopinavir/ritonavir combination, marketed as Kaletra. A major advantage is that it has two PIs in one tablet, but the major problem with the old version is that it is not heat stable. So we are obliged to store it in the fridge. As soon as the medicine is taken out of the fridge, the company says we can only handle it under 25 degrees for six weeks. We fear that most of the time it is handled at more than 30 or 35 degrees – which means after some weeks the drug's activity goes down and we have seen it even clump together so the patient can't take the drug out of the boxes anymore.

Right now we have about 100 patients in need of effective second-line treatment. And we project that by July 2006 we're going to have 140 patients. The problem is that they don't really have time, and so we need this heat-stable version of Kaletra now. We have so far reached one patient with the old version. Just to give you a practical example of how difficult it is, I'll mention his story. He really has no power at home because the power situation in Lagos is very difficult. So he needs to run generators and he has problems with the switches. So he stores the medicine in our clinic and comes on a daily basis to get his drugs. If we look into the 100 other patients in need of second-line drugs, then it becomes very, very difficult to make sure that the older version is stored under proper conditions. We really urge Abbott to make the thermal stable version available here. And as Nathan Ford mentioned before, it's ironic that African patients have no access to a second line drug designed for an African setting.

Kate Evans: I want to thank you for that and to clarify that the temperature measurements are all in Celsius. We'd like to move to Dr. Binta Biawardinai, who will speak briefly about the situation in Kenya and what the recent ministry of health there has decided versus MSF's forced protocol.

Dr. Binta

Biawardinai: Thank you, Kate. Welcome, everybody. In Kenya MSF has four HIV care programs. I worked for one year in Homa Bay. Today we are caring for 5,000 patients. Right now we have a very few number of patients taking second-line treatment, but soon we will have more and more. In Kenya, the Ministry of Health started a scaling up process for treatment in January 2005. And they released new guidelines in November 2005, which follows the WHO guidelines for ARV treatment.

MSF and many providers cannot provide the older Kaletra to many of our patients because they are too poor to buy it and the temperature in the area where we work is far above the recommended one. And we don't see how to offer better treatment to those who have enough money to buy it. So currently we are still using Nelfinavir. Of course Kaletra is better because the pill burden is less and there is no dietary restrictions – both factors that can sometimes interfere with our patients adhering to the treatment. So we really need this new heat-stable version of in Kenya.

Kate Evans: Thank you, Dr. Biawardinia. I appreciate your explaining the situation in Kenya and in particular how MSF is actually not able to follow the Ministry of Health guidelines at this point because we do not have a heat stable formulation of this critical drug available to us in Kenya. And at this point I would also like to open it up to any questions for our speakers.

Questioner 1: Thank you. Have there been any discussions with Abbott Laboratories? Is it just Abbott in this case and have there been any discussions at all and what have they said?

Kate Evans: At this point we have made a request in the beginning of the year to speak with Abbott Laboratories, specifically on their plans to distribute this new formulation outside of the U.S. and to understand what price they were going to make this drug available at. We received very vague responses, which is to say that they committed to at some point in the future pursuing registration, but insisted that registration was necessary first in Europe because of the requirement for a Certificate of Pharmaceutical Product. We looked into this issue further and have additional information available on our website which we can certainly get to you about the myth of this Certificate of Pharmaceutical Product. And what is actually the case is that Abbott, if it wanted to export this drug right now from the U.S., it could do so and request the Certificate of Pharmaceutical Product from the FDA and begin the registration process now. Instead, Abbott has taken a commercial decision to wait until the EU approval comes through so that they can export from Germany. This represents additional delays to us that are unacceptable. And so in our communications with Abbott the fact that they talk about beginning the process of registration at the end of 2006 or the beginning of 2007 are completely unacceptable because of the reasons you've heard today from Kenya and Nigeria in terms of the numbers of patients that need this drug now.

Nathan Ford: To add, we have tried to negotiate with Abbott, but what they have said to us so far has been extremely vague and non-committal. The registration issue, I can't emphasize enough how much of a blockage that is to accessing the medicine. The time between submitting the registration and getting registration in South Africa is roughly two years. And right now our understanding from Abbott is they said they were going to submit for registration the end of last year, beginning of this year, but they still today have not done so. So the longer they wait to submit, the longer we wait for the drug to be registered. And until the drug is registered it's not available at all. The second issue, of course, is price. We want a firm commitment from Abbott that they will make it available at a greatly reduced price, certainly nothing like the price that's being charged in the U.S. and Europe at the moment. And, again, we don't have any firm commitment there. So that's why we're upping the ante, so to speak, and trying to put pressure in a more public way towards Abbott. And finally, we need this drug today in our project, so we have placed an order for these medicines for a number of countries that need the drug. And we're hoping very much that Abbott will respond by ensuring that the order that we've placed will be serviced at an affordable price.

Questioner 1: Even if they agree to this, the availability would still be two years down the line? And the order that you've placed, have you placed it based on purchasing it at the present price if it's not available at a cheaper price?

Nathan Ford: I'll respond to the time question and if it's okay, I'll let Kate respond to the price question. The time between submitting and getting a drug registered differs from country to country. So when I said two years, that's roughly what it takes in South Africa. And as I've mentioned, it's also incumbent upon the companies, I think, to work to find an interim solution. So to work not just to submit the dossier and then put the burden of responsibility entirely upon drug regulatory authorities to do the registering of the drugs, but to actually work with the regulatory authorities to make sure the drug is registered as soon as possible. Avian Flu has been a good example of many dynamics in the drug market. But in South Africa it's notable that the avian flu drug, Tamiflu was registered very, very quickly, within a matter of months, in fact. So how long it takes to register a drug is also a matter of political priority and it's also a matter of to what extent drug companies cooperate in that process.

Kate Evans: And just regarding some more specifics on the order that was placed today by MSF. It is for patients treated by MSF in nine different countries, which encompasses, by the end of 2006, enough treatment for 800 of our patients. And it's really just an initial order. It does not represent the total need, but specifically the countries that were included in that list were countries in which we can easily get and have already started in many cases the process of special authorization to overcome the barrier to registration, because Abbott has not begun that process themselves. And so rather than waiting for months and years, we will go ahead and get special authorization to use this drug in country because of that need.

Regarding the price question, we're asking Abbott for a price no greater than the price they charge for the original formulation in developed countries, which is $500 per patient per year. We see no reason that the price for the new formulation should be above that and want the most affordable pricing for our patients and others.

Questioner 2: This registration process, does that mean that even if you guys get the drug from Abbott and want to distribute it, you can't? I mean, what would happen if you tried? Would it be stopped at the borders? Would it be taken out of your clinics?

Nathan Ford: So, again, to take the example from South Africa. We currently face this problem with another anti retroviral, Tenofovir. The way we access that drug is through special authorization. It's on a named-patient basis. And we have to apply for use patient by patient to the drug regulatory authorities. So it's possible and completely legal to use drugs that are not registered, but you have to go through a very complicated and lengthy bureaucratic process. MSF is an international organization and so is able to jump through all those various hoops which include also importing drugs from another country, because if a drug isn't registered then it can't be stocked in country either. But it excludes use of that drug in the public sector. So we're using Tenofovir today, but most of our public sector physician counterparts are completely unable to use that drug and they have to wait for registration. And it will be the same case for the new Kaletra. We will be able to use that drug legally but it won't be a mechanism that will make the drug more broadly available.

Questioner 2: And can I just follow up? Where are you with Gilead on your fight about Tenofovir?

Nathan Ford: We're still waiting for the drug to be registered and we're still waiting for Gilead to propose an interim solution that is more quick and cost effective than having to ship the drug from California.

Daniel Berman (MSF's Access to Essential Medicines Campaign):

Can I address that question? Regarding Gilead, one of the problems is they had given voluntary license to Aspen, which is a generic drug company in South Africa. Aspen needs to file for registration. So the company had two paths. One would have been that they could have registered the existing product and it would have already been on the market in South Africa and other countries. But in fact they've waited for this generic company and so far the company, Aspen, doesn't even have a product that they can request registration for.

So, in other words, Gilead still has not even filed in many of the countries in Africa and they haven't even started that process. So I think we have a similar problem in terms of Gillead as we do with Abbott.

Questioner 3: Is Kaletra used only as second line therapy or is it used as first line therapy in its present formulation? And can somebody explain -- I thought I read in the letter that this is actually a cheaper process – to make it heat resistant. So I'm curious about that.

Daniel Berman: I can try to address both questions. First, there was a group of experts who met at the World Health Organization in July. And the WHO is going to be releasing new guidelines for resource poor settings. The draft of that is already available on their website. And it recommends only boosted protease inhibitors, ones that have ritonovir in them for a second line. So the clear answer is that this drug is recommended for second line. The situation we have now is that the drug we have been using is no longer recommended. We had been using Nelfinavir because it's the only one that you don't have to refrigerate. But the new guidelines say that that's not recommended anymore. They recommend boosted drugs, and the only boosted one that doesn't have to be refrigerated is this new version of lopinavir/ritonavir.

Kate Evans: I would just like to add that those guidelines are specific, as Daniel said, to resource-poor settings. So in the U.S. and Europe you may find people living with HIV who are taking lopinavir/ritonavir as their first-line medication.

Daniel Berman: And regarding the cost of production. We did some investigation. Of course, MSF doesn't have the expertise to know about production. So we went to the experts. We went to the World Health Organization. We went to Chinese drug manufacturers and we went to Brazilian drug manufacturers. And they all had the same conclusion that this technology at high volumes would have a lower cost of production per unit. And very simply put, that's because the technology is actually put several steps into one machine and so you don't have the loss of the product between each step. That's one of the key reasons. And so the experts say that at high volumes this product would be less expensive to make.

Questioner 3: Just a quick follow up on that then. Are you suggesting then that once this heat resistant formulation of Kaletra is available that this will become first-line therapy?

Daniel Berman: No. What I was saying is that the guidelines talk about use of protease inhibitors as second-line. And I think what Kate was referring to was that in the U.S. and in Europe patient care is more individualized and physicians may decide to put patients on protease inhibitors as first-line. But I think there's more or less a trend to use non-nucleotides as first-line and to save the protease inhibitors. I think that's the way things are moving in general. And in terms of the WHO guidelines, they've actually put that into writing and said that these drugs are meant for second line. That's their recommendation.

Questioner 1: Does anyone know whether any of these drugs are available through PEPFAR, the second line treatments. Do they make them available?

Kate Evans: I can answer that to a certain degree, but part of the answer is no. PEPFAR at this point does use Tenofovir. And we have been speaking with representatives of PEPFAR, particularly regarding the use of heat stable lopinavir/ritonavir to see if grantees would be importing that drug and that that would be a way to accelerate access through the PEPFAR program. At this point they have no plans to make special use of the new heat stable lopinavir/ritonavir, although this could change if particular care providers wanted to make sure that this drug was available to their patients.

Daniel Berman: I think that that for us is a real problem: that the U.S. government is sending the old formulation which we know is not adapted to a lot of places, because as we said, it melts at high temperatures. So it's a real problem that the U.S. government is paying for the old formulation and not pushing for the new formulation.

Kate Evans: I'd like to thank everybody for staying with us and we will follow up with any additional information.

###

Heather L. Mason
Vice President International
Marketing

200 Abbott Park Road
D6MP, AP34-3
Abbott Park, IL 60064

March 17, 2006

Nicolas de Torrente
Executive Director
MSF-USA
333 Seventh Avenue, 2nd Floor
New York, NY 10001-5004

Dear Mr. de Torrente:

We received your letter dated March 15, 2006. We want to be clear about patients' access to Abbott's lopinavir/ritonavir in developing countries and to confirm our commitment to achieving accelerated approvals for the new formulation.

Patients in need of second-line treatment in the countries you mentioned have ready access to our lopinavir/ritonavir capsules. Thus, to suggest patients may have to be left untreated is not responsible. In fact, the number of patients treated in the last year on lopinavir/ritonavir capsules in Africa nearly doubled.

We share your excitement about the benefits of the new tablet formulation and its importance to patients. This innovative, unique and complex technology has significant advantages for patients. We have been actively working with governments to secure rapid regulatory approval. For example, South Africa has granted our request for fast track registration of the lopinavir/ritonavir tablets.

Your letter mentions that MSF is acquiring necessary authorizations from regulatory authorities to import unregistered product into several developing countries. Once we receive the official approval for such import, granted by the proper regulatory authorities, we will be glad to discuss shipping tablets into those respective locations. We stand ready to meet with MSF or any other organizations to achieve rapid regulatory approval to benefit patients.

Sincerely,

Heather L. Mason
Vice President International Marketing
Abbott International

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Réponse publique à la lettre du laboratoire Abbott adressée à MSF le 17 mars 2006

23 mars 2006,

Miles White
Chairman and CEO
Abbott Laboratories
200 Abbott Park Rd.
Abbott Park, IL 60064-6189

Envoyée par fax et email

Monsieur,

Nous avons reçu une lettre de Mme Heather Mason des laboratoires Abbott datée du 17 mars 2006. Au nom de Médecins Sans Frontières, je souhaite répondre à un certain nombre de questions soulevées dans cette lettre. Je vous demande également de nous apporter une réponse claire sur la volonté d'Abbott d'honorer la commande émise par MSF le 15 mars 2006 (ordre d'achat numéro 31556) de 4.762 boîtes de lopinavir/ritonavir thermostable au prix maximum de 500 $ par patient et par an.

Abbott écrit que les patients dans les pays pour lesquels nous avons passé commande de cette nouvelle version de lopinavir/ritonavir (LPV/r) ont un accès facile à l'ancienne version (sous forme de gélule souple). Suggérer que cela constitue une solution adéquate, en attendant qu'Abbott rende disponible la nouvelle version thermostable en comprimé, ignore les contraintes pratiques qui ont motivé la commande de MSF. La nécessité de réfrigérer l'ancienne formulation de lopinavir/ritonavir rend celle-ci virtuellement impossible à utiliser dans la plupart des programmes MSF. De plus, dans les pays à revenus intermédiaires, comme la Thaïlande et le Guatemala, le prix demandé par Abbott rend cette ancienne version inaccessible à la fois aux gouvernements et aux patients. Aujourd'hui, la nouvelle version thermostable de lopinavir/ritonavir est le seul inhibiteur de protéase boosté adapté aux conditions du terrain. MSF continue d'appeler Abbott à tout faire pour accélérer la disponibilité de cette nouvelle formulation dans les pays en développement.

MSF s'inquiète de voir Abbott multiplier les obstacles, et subordonner toute discussion concernant l'exécution de la commande au fait que MSF fasse la preuve de l'obtention d'une autorisation spéciale dans chaque pays. Certains, comme le Kenya et l'Ouganda, exigent pour délivrer une telle autorisation une confirmation de la commande, indiquant le numéro de lot, le prix, la date de livraison et l'origine du chargement. Le retard pris par Abbott pour fournir ces informations empêche MSF, qui dispose d'une expérience approfondie des autorisations nécessaires permettant l'importation de médicaments qui ne sont pas encore enregistrés, de démarrer les démarches nécessaires pour l'obtention de ces autorisations.

MSF a demandé que notre commande soit livrée à MSF Logistique, le centre d'approvisionnement de MSF, centrale d'achat pharmaceutique sous douane en France, afin que le processus d'enregistrement de la commande et l'obtention des autorisations spéciales puissent être organisés simultanément et ainsi éviter des délais inutiles. Bien que nous ne fassions aucune objection pour partager les documents d'autorisation spéciale avec vous, aucune réglementation n'empêche Abbott d'acheminer la version thermostable de lopinavir/ritonavir dans l'entrepôt de MSF. D'autres compagnies expédient régulièrement des médicaments à MSF Logistique.

Dans votre lettre, Abbott fait état de son intention « d'obtenir une approbation réglementaire rapide pour le bénéfice des patients ». Toutefois, Abbott n'a pas indiqué de changement de politique pour commencer immédiatement à déposer des dossiers d'enregistrement de son médicament dans les pays en développement. Abbott a publiquement déclaré avoir besoin d'un Certificat de Produit Pharmaceutique (CPP) de l'Union Européenne pour enregistrer son produit en Afrique, arguant que la nouvelle version de lopinavir/ritonavir est fabriquée en Allemagne. Cependant, un CPP n'est pas requis dans tous les pays en développement, et pour les autorités de régulation qui demanderaient un CPP, ce document pourrait être émis par la *Food and Drug Administration* des Etats-Unis (US FDA), si Abbott décidait d'exporter son produit des Etats-Unis. Ainsi, il n'existe aucun obstacle pour commencer le processus d'enregistrement dans les pays en développement. MSF exhorte à nouveau Abbott à démarrer immédiatement ce processus.

La confirmation par les laboratoires Abbott, le 13 mars, du développement d'une formulation thermostable de ritonavir, est une nouvelle encourageante pour MSF. L'accès au ritonavir thermostable offrirait aux personnels soignants d'autres options que la nouvelle formulation de lopinavir/ritonavir. Selon les prochaines recommandations de l'Organisation Mondiale de la Santé, le ritonavir thermostable peut être associé à d'autres inhibiteurs de protéase thermostables, produits par d'autres compagnies pharmaceutiques et disponibles à un prix abordable. MSF souhaiterait connaître la date prévue de mise à disposition de cette nouvelle formulation.

MSF appelle Abbott à prendre les mesures nécessaires pour honorer la commande de MSF et rendre disponible, à un prix abordable, la nouvelle formulation thermostable de lopinavir/ritonavir dans les pays en développement, comme l'ont demandé de nombreux chercheurs, des soignants et des organisations de lutte contre le sida, dans une lettre qui vous a été adressée le 15 mars 2006.

Je reste, comme toujours, disponible pour vous rencontrer personnellement et attends une réponse rapide de votre part.

Je vous prie d'agréer, Monsieur, l'expression de mes salutations distinguées,

Nicolas de Torrente
Directeur Général

cc:
Heather Mason, Vice President, International Marketing, Abbott Laboratories
Robert Dintruff, Director, Global Cares Initiative, Abbott Laboratories
Rita Roy, Global Citizen Shop, Abbott Laboratories

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Open Response to Abbott Laboratories' Letter to MSF on March 17, 2006

March 23, 2006

Miles White
Chairman and CEO
Abbott Laboratories
200 Abbott Park Rd.
Abbott Park, IL 60064-6189

Sent via facsimile and email

Dear Mr. White,

We received a letter from Ms. Heather Mason of Abbott Laboratories dated March 17, 2006. On behalf of Doctors Without Borders/Médecins Sans Frontières (MSF), I would like to respond to a number of the issues raised in this letter and request a clear response regarding whether or not Abbott will fulfill MSF's order (purchase order number 31556) of 4,762 bottles of heat-stable lopinavir/ritonavir at the cost of no more than $500 per patient per year placed on March 15, 2006.

Abbott writes that patients in the countries for which we have ordered the new version of lopinavir/ritonavir (LPV/r) have ready access to the old, soft-gel version. To suggest that this is an adequate interim solution until Abbott makes the new heat-stable tablet formulation available in developing countries ignores the practical constraints that form the basis for MSF's order. The refrigeration requirement for the old lopinavir/ritonavir formulation makes it virtually impossible to use in many of MSF's projects. Furthermore, in middle-income countries, such as Thailand and Guatemala, the price Abbott charges for the old version makes it inaccessible to both the government and individual patients. At present, the new heat-stable lopinavir/ritonavir is the only field-adapted, boosted protease-inhibitor, and so MSF continues to urge Abbott to take action to accelerate access to this formulation in developing countries.

MSF is concerned that Abbott is introducing additional obstacles by making any discussion of the fulfillment of MSF's order contingent on proof of MSF's acquisition of special authorizations in each country. Some countries, such as Kenya and Uganda, request an order confirmation indicating batch number, price, date of delivery, and origin of shipment to obtain this authorization. Abbott's delay in providing this information prevents MSF from taking the necessary steps to request special authorizations. MSF has extensive experience acquiring the necessary authorizations whenever we import unregistered medicines.

MSF has requested that our order be delivered to MSF's procurement center (MSF Logistique), a bonded pharmaceutical warehouse in France so that the process of fulfilling the order and securing special authorizations can occur simultaneously, to avoid unnecessary delays. While we have no objection to sharing special authorization documentation with you, there are no legal or regulatory requirements that

prevent Abbott from shipping heat-stable lopinavir/ritonavir to MSF's warehouse. Other companies regularly ship medicines to MSF Logistique.

In your letter, Abbott states its intention "to achieve rapid regulatory approval to benefit patients." However, Abbott has not indicated a policy change to immediately begin filing for registration in developing countries. Abbott has publicly stated that it needs a Certificate of Pharmaceutical Product (CPP) from the European Union in order to register the drug in African countries because the new version of lopinavir/ritonavir is manufactured in a plant in Germany. Yet, a CPP is not required in all developing countries, and for the regulatory authorities that do require a CPP, this document could be generated by the US FDA if Abbott chose to export from the US. Therefore, there is no barrier to filing for registration in developing countries, and MSF again urges Abbott to immediately begin filing for registration.

MSF was encouraged to receive confirmation from Abbott Laboratories on March 13 that it is developing a heat-stable formulation of ritonavir. Access to heat-stable ritonavir will give care providers options other than new lopinavir/ritonavir. As per the forthcoming WHO guidelines, they can pair this with other available and affordable, heat-stable protease-inhibitors produced by other pharmaceutical companies. MSF would like to know the target date for availability of this new formulation.

MSF calls on Abbott to take the necessary steps to fulfill MSF's order and make heat-stable lopinavir/ritonavir available and affordable in developing countries as numerous HIV/AIDS researchers, care-providers and treatment advocates urged in a letter to you dated March 15, 2006. As always, I am available to meet with you personally, and I look forward to your prompt response.

Sincerely,

Nicolas de Torrente
Executive Director

cc:
Heather Mason, Vice President, International Marketing, Abbott Laboratories
Robert Dintruff, Director, Global Cares Initiative, Abbott Laboratories
Rita Roy, Global Citizen Shop, Abbott Laboratories

ABBOTT's NEW AND IMPROVED KALETRA: ONLY IN THE US … BUT WHAT ABOUT THE REST OF THE WORLD?

Briefing Note
Médecins Sans Frontières (MSF)
February 2006

Médecins Sans Frontières (MSF) is deeply concerned that Abbott's new version of the second-line fixed dose combination lopinavir/ritonavir – LPV/r, marketed as Kaletra, is not available in developing countries. The US Food and Drug Administration (FDA) approved a new version of LPV/r in October 2005 that has critically important advantages for patients in developing countries: lower pill count [down from six to four per day], storage without refrigeration, and no dietary restrictions. Some MSF projects have an urgent need for this drug, as no other boosted protease inhibitors – the cornerstone of second-line therapy - are practical to use in the hot climates of many developing countries, where refrigeration is not readily available.

New LPV/r is available in the US, but not in any developing countries and there is no publicized differential price or system of distribution for developing countries. If made accessible and affordable, the new and improved version of LPV/r could offer major benefits to patients across the developing world.

In 2005, approximately six percent of MSF patients that had been on treatment for three years were on second-line drugs, and in one MSF program that has access to viral load monitoring, after four years of treatment, 16% of patients needed a new combination. These data underline the acute and growing need for access to newer, field-adapted second-line drugs. But new LPV/r remains out of reach to MSF medical professionals and others working in developing countries. Without access to this drug, there is no practical solution for patients who no longer can benefit from older first-line drugs.

Because Abbott Laboratories is the sole producer of the new LPV/r and no generic versions have been internationally validated, MSF and others are dependent on the willingness of the company to make this urgently needed drug widely available.

MSF therefore calls on Abbott to:

- **Register the new version of LPV/r in developing countries and replace the old version of LPV/r with the new one, as they have already done in the US;**
- **Set an affordable differential price for the new formulation of LPV/r in developing countries, at the same level or lower than the price for the previous version ($500 per year per patient);**
- **Include middle-income countries as beneficiaries of the differential price; and**
- **Eliminate patent barriers to production of generic versions of new LPV/r for use in developing countries.**

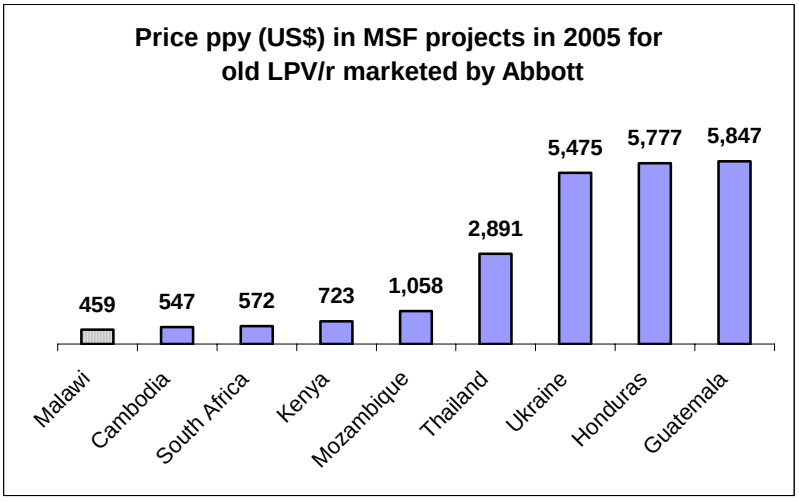
BACKGROUND

An Essential Medicine for Second-Line Treatment

Lopinavir/ritonavir (LPV/r) has been recognized as an essential medicine by the WHO,[i] as it is the only co-formulation that consists of a protease inhibitor (lopinavir) and booster (ritonavir) in the same pill. The WHO will include LPV/r in its revised recommendations[ii] as part of a second-line therapy once first-line treatment failure has occurred. Abbott Laboratories has been marketing the old formulation of LPV/r as Kaletra since 2000. But the old version of LPV/r has some serious drawbacks, as it requires refrigeration, comes with a high pill burden of six capsules per day and needs to be taken with food. Although second-line regimens including LPV/r are preferred in developing countries, they have not been an option in many places because of the the refrigeration requirement of the old formulation. The 14th WHO Expert Committee on the Use of Essential Medicines recommended the use of " *fixed dose combinations and the development of appropriate new FDCs, [which include] modified dosage forms,* ***non-refrigerated formulations*** *…*"[iii]

Price for Developing Countries Should Be the Same As, or Less Than, the Old Version

Since May 2002, Abbott has been selling the old formulation of LPV/r in Africa and Least Developed Countries for $500 per patient per year on an FOB basis (meaning that freight, insurance, customs handling, taxes and duties paid by purchaser). However, unlike other companies, Abbott does not offer differential prices in middle-income countries even though in these countries millions live on less than US $2 per day. As the chart below shows, middle-income countries are paying dearly for access to the old formulation of LPV/r.



The price of LPV/r in middle-income countries outside Africa is on average 7.4 times more expensive than in low-income countries (mean: $672 vs. $4,998). In some developing countries, the price for the old version of LPV/r is nearly as high as it was in the US ($6,944).

In Brazil, where the government has twice threatened to manufacture the drug at a lower cost under a compulsory license, Abbott Laboratories agreed to cut the price of old LPV/r formulation from $2,562 to $1,379 per patient/year, starting in March 2006[iv]. Although this is an improvement, Brazil will still have to pay nearly three times the price of the old formulation of LPV/r in Africa and least-developed countries.

In the Long Run, Alternate Suppliers Will Be Critical

There is currently some generic production of the old formulation of LPV/r, but the sources have not been internationally validated yet, and patents on the combination could block companies from marketing it in some countries. In addition, new patent obstacles may prevent the development of generic versions of the new formulation of LPV/r. Given the usual patenting strategies of multinational pharmaceutical companies, the new formulation of LPV/r is likely to be patent protected in drug producing countries for a new 20 year period, preventing generic competition.

Registration Should Be Immediately Sought For New Formulation

The old formulation of LPV/r (133/33.3 mg soft gel capsules) is registered in 54 countries and registration is pending in 14 others, covering 68 of the 69 countries eligible for Abbott's Access Program. But the new formulation of the drug has not been registered in any country except for the US. MSF calls on Abbott to register the new formulation of LPV/r (200/50 mg tablets) promptly and replace the old version with the new one in developing countries, as they have done in the US**.**

THE BOTTOM LINE:
The new formulation of LPV/r represents a significant improvement in second-line options for ARV treatment in developing countries. Abbott needs to make new LPV/r available throughout the developing world at an affordable price without further delay.

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[i] 14th edition, WHO Model List of Essential Medicines (revised March 2005)
[ii] Summary is available for consultation at http://www.who.int/3by5/mediacentre/news51/en/
[iii] 14th edition, WHO Model List of Essential Medicines (revised March 2005)
[iv] H*http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=1&DR_ID=33054H* Reported October 12, 2005

UNNECESSARY DELAYS BY ABBOTT:
THE "CPP" MYTH DEBUNKED

10 MARCH 2006

MSF needs the new and improved version of LPV/r (lopinavir/ritonavir) for its AIDS projects now – the drug is a crucial component of second-line antiretroviral therapy, and is particularly important for use in many developing counties where MSF operates, since it no longer requires refrigeration, as the old version does. Today this heat-stable, fixed-dose combination is only available in the US.

However, Abbott has not begun the process of registering this drug in developing countries and claims that this process cannot begin until the drug is registered in Europe. This document explains why the company does not need to wait but instead could begin filing for registration in developing countries now.

Abbott claims that a Certificate of Pharmaceutical Product (CPP) must be issued from Europe in order to register the new formulation in developing countries. We claim that this is a choice. According to WHO, the CPP must be issued by the exporting country and therefore could be issued today by the US FDA. (www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/index.html)

What is a Certificate of Pharmaceutical Product?
The CPP is one part of a multi-pronged strategy to improve national drug authorities' ability to regulate products by creating a standard that clearly communicates a drug's status with respect to marketing authority and manufacturing standards. Essentially the CPP says, "yes we (e.g. the US FDA) have registered this product as safe for sale in our country and we inspect and have confidence in the manufacturing practices of the producer." Not all countries even require a CPP to register a drug for use, but those that do, require it from the exporting country. For instance, Abbott has said it will file for registration of the new LPV/r formulation in South Africa – the only developing country the company has slated for registration so far – where the drug regulatory authority does not require a CPP for registration. Abbott could file for registration in all developing countries, and if a country does require a CPP, it could be issued from the US drug regulatory authorities.

Reading Between the Lines: The facts about the CPP
Abbott says it needs an EU CPP in order to register the drug in African countries, because the new version of LPV/r is manufactured in a plant in Germany. But the key point here is not where the drug is produced, but from which country it will be exported. Abbott may want to export this product from Europe instead of from the US, but this is a commercial decision, NOT a regulatory requirement. New LPV/r was approved by the US FDA in October 2005, and is available only in the US right now. MSF has confirmed that the US FDA inspects the manufacturing plant in Germany where the product is manufactured and has been assured that the FDA could issue a CPP.

The Bottom Line:

As not every country requires a CPP for registration, Abbott should immediately register the drug in those countries that do not require a CPP, and should obtain a US CPP to expedite registration in countries that do.

Does the CPP issue affect individual shipments, in the period before the drug is registered?
No. Because MSF and other organisations and institutions will obtain special authorization to get new LPV/r to HIV/AIDS projects, the CPP is a requirement related to registration but not special authorisation to import.