

JOSE LLORED CAMACHO & CO.

ABOGADOS

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E.

S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-089792- -00010-0000

Fecha: 2012-06-05 15:42:11 Dep. 2020 DIR.NUEVASCR
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Act. 523 RESPUESTA Folios: 29

Re: PI.-ABBOTT LABORATORIES.-Solicitud de Patente de Invención en Fase Nacional PCT para "UNA FORMULACIÓN SÓLIDA DE DOSIFICACIÓN FARMACÉUTICA QUE COMPRENDE UNA SOLUCIÓN O DISPERSIÓN SÓLIDA DE LOPINAVIR Y RITONAVIR".-Clase A61K 31/513.- Expediente número 07-089.792.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 9 de Marzo de 2012.

2. Con el fin de responder las objeciones expuestas por el Señor Examinador en su Concepto Técnico correspondiente al Oficio No. **03700**, en relación a la Claridad del Título y del Capítulo Reivindicatorio actualmente en estudio y a la Novedad de la presente solicitud, me permito dirigir su atención a las siguientes modificaciones y argumentos técnicos por medio de los cuales se superan completamente dichas objeciones.

3. **TÍTULO DE LA SOLICITUD.**

Con respecto al título de la solicitud, el Señor Examinador señala que este no se relacionaría adecuadamente con el objeto reclamado por el capítulo reivindicatorio, y sugiere modificarlo para hacerlo más cercano a la materia sobre la cual se busca protección.

Atendiendo esta sugerencia, me permito manifestar que es deseo del solicitante modificar el título de la solicitud para hacer que este describa de forma más precisa el objeto de la invención.

Así, el nuevo título se lee como sigue:

"UNA FORMULACIÓN SÓLIDA DE DOSIFICACIÓN FARMACÉUTICA QUE COMPRENDE UNA SOLUCIÓN O DISPERSIÓN SÓLIDA DE LOPINAVIR Y RITONAVIR"

De esta forma este nuevo título describe de manera clara el objeto de la invención, y por lo tanto supera completamente las objeciones que en este sentido presentó el Señor Examinador.

4. **CLARIDAD DEL CAPÍTULO REIVINDICATORIO.**

De otra parte, el Señor Examinador objeta la claridad del capítulo reivindicatorio actualmente presentado, señalando que este no caracteriza de manera adecuada el objeto de la invención, e incluye términos imprecisos.

Tomando en consideración estas objeciones me permito manifestar que es deseo del solicitante presentar un **nuevo capítulo reivindicatorio**, que reemplaza al anterior, el cual describe de manera clara y concisa la forma de dosificación farmacéutica de la invención, haciendo referencia a sus características técnicas esenciales.

Con respecto al mencionado nuevo capítulo reivindicatorio me permito resaltar que este no constituye de ninguna manera una ampliación al alcance de la invención, tal como fue originalmente presentada, toda vez que se está definiendo la forma de dosificación farmacéutica de acuerdo con las revelaciones de la descripción de la solicitud, como se muestra a continuación:

- **Reivindicación 1.** Esta reivindicación tiene como base la reivindicación 1 actualmente presentada, en la cual se incluyeron características particulares de las realizaciones preferidas de la invención como la cantidad de principio activo y de tensoactivo contenidas, tal como se encontraban en la reivindicación 3 actualmente presentada.
- **Reivindicación 2.** Corresponde a la reivindicación 4 actualmente presentada.
- **Reivindicaciones 3 y 4.** Las nuevas reivindicaciones 3 y 4 corresponden a las reivindicaciones 7 y 8 actualmente presentadas.
- **Reivindicación 5.** La nueva reivindicación 5 se refiere un tipo de solución sólida preferido de la invención.

De esta forma, el nuevo capítulo reivindicatorio está constituido por **5 reivindicaciones**, la cuales describen de manera clara y concisa la forma de dosificación farmacéutica objeto de la presente invención, haciendo referencia a las características técnicas esenciales de acuerdo con las enseñanzas de la descripción.

Consecuentemente, el nuevo capítulo reivindicatorio aquí presentado se enmarca completamente dentro de lo estipulado por el Artículo 30 de la Decisión Andina 486 de 2000.

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5. NOVEDAD.

Finalmente, el Señor Examinador indica que la materia reclamada por la solicitud en estudio sería anticipada por las enseñanzas del documento **CO2006019306 (D3)**.

En este sentido el Señor Examinador asegura que todas las características técnicas de la invención estarían reveladas en dicho documento D3.

A este respecto me permito señalar que si bien existen similitudes entre las enseñanzas del documento D3 y la forma de dosificación farmacéutica de la invención, dicho documento no revela una composición como la que es ahora definida por la reivindicación 1, y mucho menos una composición que pueda ser empleada sin alimento.

En este sentido es pertinente resaltar que el solicitante ha descubierto de manera sorprendente que específicamente la composición de la invención puede ser administrada sin alimento, contrario a lo que era usual en el estado del arte. Así, en la dentro de la ficha técnica del producto comercial Kaletra (página 5, documento anexo al presente memorial), se muestra que las formulaciones anteriores a la de la presente invención debían siempre ser tomadas con comida, debido a que sin esta la cápsula o solución oral de Kaletra tiene una exposición de medicamento (medida en AUC) que es al menos 50% más baja que la obtenida al ser administrada con alimento.

Contrario a lo anterior, la formulación desarrollada en la presente invención tiene una exposición de medicamento comparable con o sin comida, como se demuestra en las figuras que hacen parte de la descripción de la solicitud.

En conexión con lo anterior me permito llamar la atención a ese Despacho al hecho que el efecto de los alimentos sobre un medicamento no es de ninguna manera predecible, tal como sería claro para la persona versada en la materia. Por ejemplo dentro de las Guías de la FDA para la industria (Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies, CDER, December, 2002, página 2, anexo al presente memorial) se señala que:

"Para otros productos de liberación inmediata de medicamento (BCS Clases II, III y IV) y para todos los productos de liberación modificada de medicamento, los efectos de los alimentos son muy probablemente resultado de una combinación más compleja de factores que influyen la disolución in vivo de un producto de medicamento y/o la absorción de la sustancia de medicamento. En estos casos, la dirección y magnitud relativas de los efectos de los alimentos en la biodisponibilidad de la formulación y los efectos en la demostración de la bioequivalencia son difíciles, sino imposibles, de predecir sin conducir un estudio de bioequivalencia con alimentación."

Si se toma en consideración que el lopinavir es un medicamento conocido por pertenecer a la clasificación BCS II/IV debido a su baja solubilidad (tal como se describe en el documento Lindenber g, M. *European Journal of Pharmaceutics and Biopharmaceutics*, (58) 2004, 265-278, anexo al presente memorial), es claro que los efectos de la ingesta de comida en el nivel plasmático de este medicamento no son predecibles y es aquí donde la presente invención proporciona un novedoso aporte al estado de la técnica.

Consecuentemente, el arte previo no describe una forma de dosificación que comprenda todas las características técnicas de la presente invención y por lo tanto, la solicitud en estudio claramente se ajusta a lo preceptuado pro el Artículo 16 de la Decisión Andina 486 de 2000.

6. **CONCLUSIÓN.**

Para finalizar me permito resaltar que el nuevo título de la solicitud refleja de manera más cercana la materia reclamada.

Así mismo, de lo discutido anteriormente es evidente que el nuevo capítulo reivindicatorio presentado junto con este memorial es totalmente claro y conciso al reclamar la forma de dosificación farmacéutica de la invención, refiriéndose a sus características técnicas esenciales.

Por otro lado, a la luz de este nuevo capítulo reivindicatorio, y en virtud de los argumentos discutidos con respecto al documento D3, se estableció de manera incontrovertible la Novedad de la solicitud en estudio frente al estado del arte más próximo.

7. Anexo me permito presentar:

(i) Copia de la página **61** que corresponde al **nuevo capítulo reivindicatorio**, discutido en el presente memorial, constituido por **5** reivindicaciones;

(ii) Copia de la ficha técnica del producto comercial Kaletra;

(iii) Copia de la portada y las páginas 1 a 9 del documento *Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies*, CDER, December, 2002; y

(iv) Copia del documento Lindenber g, M. *European Journal of Pharmaceutics and Biopharmaceutics*, (58) 2004, 265-278.

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8. En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las modificaciones y los argumentos presentados y conceder el privilegio de patente solicitado.

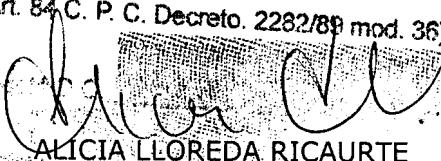
Señor Superintendente,

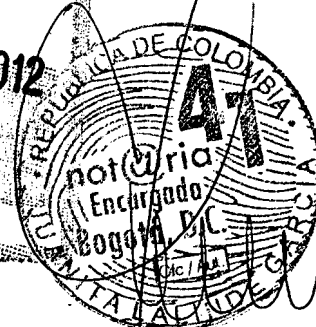

ALICIA LLORED RICAURTE
T.P. 53.215

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció personalmente: Alicia Lloreda Ricaurte
identificada (a) con: CC 39.690.713
profesional de abogado No. 53215 del Consejo Superior de la Judicatura, quien autentica la firma puesta por ella (el) mismo en este escrito.
(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

30 MAYO 2012


ALICIA LLORED RICAURTE
C.C. No. 39.690.713 de Usaquén



REIVINDICACIONES

1. Una forma sólida de dosificación farmacéutica para su uso en el tratamiento de VIH, donde dicha forma de dosificación se administra sin alimento y comprende una solución sólida o una dispersión sólida de lopinavir y ritonavir en un polímero soluble en agua farmacéuticamente aceptable, y un tensoactivo farmacéuticamente aceptable,

donde dicho polímero soluble en agua es un homopolímero o copolímero de N-vinil pirrolidona y dicho tensoactivo es monolaurato de sorbitán o monopalmitato de sorbitan, y donde el lopinavir y el ritonavir están presentes en una cantidad de 5 a 30% en peso de la forma de dosificación farmacéutica, y donde dicho surfactante está presente en una cantidad de 2 a 20% en peso de la forma de dosificación .

2. La forma de dosificación de la reivindicación 1, donde dicha solución sólida o dispersión sólida es una solución sólida.

3. La forma de dosificación de la reivindicación 1, donde dicho polímero soluble en agua es copovidona, y dicho tensoactivo comprende monolaurato de sorbitán.

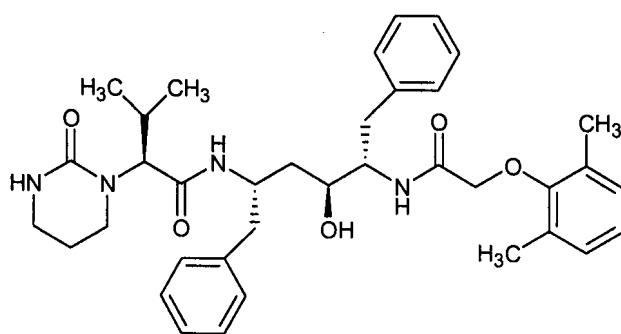
4. La forma de dosificación de la reivindicación 3, donde dicha solución sólida o dispersión sólida es una solución sólida.

5. La forma de dosificación de la reivindicación 3, donde dicha solución sólida o dispersión sólida es una solución vítrea.

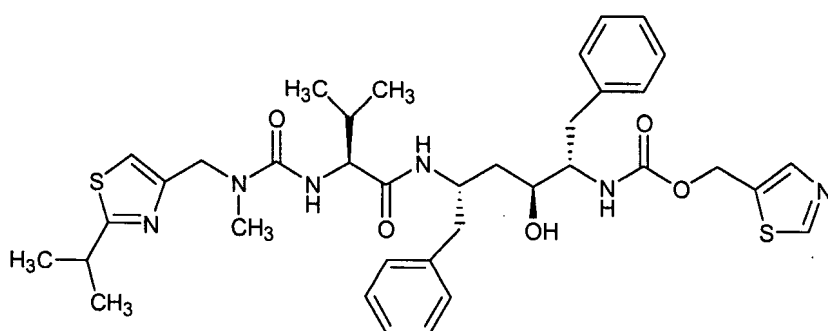
(Nos. 3956 and 3959)
NEW**KALETRA™**(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution**R_x** only**DESCRIPTION**

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

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is C₃₇H₄₈N₄O₅, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is C₃₇H₄₈N₆O₅S₂, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

KALETRA capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA oral solution contains 42.4% alcohol (v/v).

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of action: Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006 – 0.017 $\mu\text{g/mL}$, 1 $\mu\text{g/mL}$ = 1.6 μM) and ranged from 4-11 nM (0.003 – 0.007 $\mu\text{g/mL}$) against several HIV-1 clinical isolates ($n=6$). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 – 289 nM (0.04 – 0.18 $\mu\text{g/mL}$), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance: HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to KALETRA in antiretroviral treatment naive patients has not yet been characterized. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. The assessment of these mutational patterns is under study.

Cross-resistance - Preclinical Studies: Varying degrees of cross-resistance have been observed among protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed >4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed <4-fold reduced susceptibility to lopinavir. Isolates with >4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor therapy. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naïve patients with HIV RNA >1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). The EC₅₀ of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC₅₀ against wild type HIV. Fifty-five percent of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir with a mean reduction in lopinavir susceptibility of 27.9-fold.

After 24 weeks of treatment with KALETRA, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤400 copies/mL was observed in 93% (27/29) and 65% (15/23) of patients with <10-fold and ≥10-fold reduced susceptibility to lopinavir at baseline, respectively.

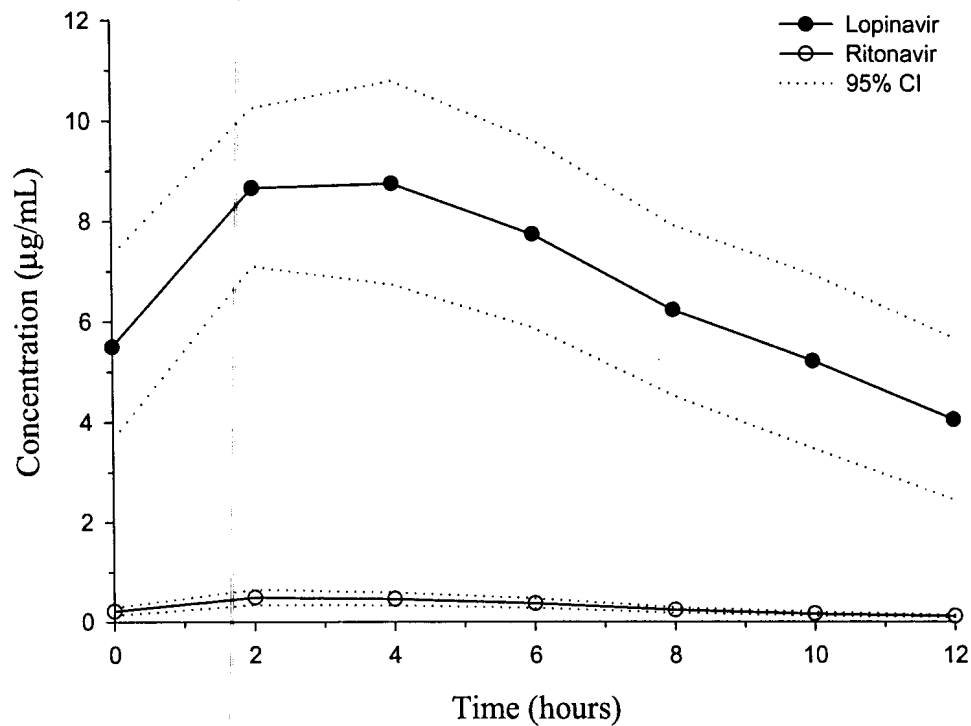
In addition, virologic response was observed in 96% (24/25) of patients whose baseline viral isolates contained up to 5 mutations recognized to be associated with protease inhibitor resistance. Fourteen of those 25 isolates contained mutations at positions 82, 84 and/or 90. Virologic response was observed in 67% (18/27) of patients whose baseline viral isolates contained 6 or more mutations, including those at positions 82, 84 and/or 90 plus multiple other mutations. There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Pharmacokinetics

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

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg BID for 3-4 weeks from a pharmacokinetic study in HIV-infected adult subjects (n=21).

Figure 1
Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 21)



Absorption: In a pharmacokinetic study in HIV-positive subjects (n=21) without meal restrictions, multiple dosing with 400/100 mg KALETRA BID for 3 to 4 weeks produced a mean $\pm$ SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

Effects of Food on Oral Absorption: Administration of a single 400/100 mg dose of KALETRA capsules with a moderate fat meal (500-682 Kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max} , respectively, relative to fasting. For KALETRA oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of KALETRA with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability KALETRA should be taken with food.

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

Metabolism: *In vitro* experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C -lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination: Following a 400/100 mg ^{14}C -lopinavir/ritonavir dose, approximately $10.4 \pm 2.3\%$ and $82.6 \pm 2.5\%$ of an administered dose of ^{14}C -lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The half-life of lopinavir over a 12 hour dosing interval averaged 5-6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 L/h.

Special Populations:

Gender, Race and Age: Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pediatric Patients: The pharmacokinetics of KALETRA 300/75 mg/m² BID and 230/57.5 mg/m² BID have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m² BID regimen without nevirapine and the 300/75 mg/m² BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max} , and C_{min} were $72.6 \pm 31.1 \mu g \cdot h/mL$, 8.2 ± 2.9 and $3.4 \pm 2.1 \mu g/mL$, respectively after KALETRA 230/57.5 mg/m² BID without nevirapine (n=12), and were $85.8 \pm 36.9 \mu g \cdot h/mL$, 10.0 ± 3.3 and 3.6 ± 3.5

µg/mL, respectively after 300/75 mg/m² BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (3 months to 8 years) or 4 mg/kg BID (>8 years).

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

Hepatic Impairment: Lopinavir is principally metabolized and eliminated by the liver. Although KALETRA has not been studied in patients with hepatic impairment, lopinavir concentrations may be increased in these patients (see **PRECAUTIONS**).

Drug-Drug Interactions: See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS: Drug Interactions**.

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS**).

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA 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.

KALETRA is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 1 (effect of other drugs on lopinavir) and Table 2 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 6 in **PRECAUTIONS**.

Table 1: Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Amprenavir ¹	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	0.89 (0.83, 0.95)	0.85 (0.81, 0.90)	0.81 (0.74, 0.89)
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz ²	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nevirapine	200 QD, 14 days; BID, 6 days	400/100 BID, 20 d	5, 9*	0.95 (0.73, 1.25)	0.99 (0.74, 1.32)	1.02 (0.68, 1.53)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk ³	300/75 mg/m ² BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 QD, 10 d	400/100 BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
Ritonavir ⁴	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

¹ Composite effect of amprenavir 450 and 750 mg Q12h regimens on lopinavir pharmacokinetics.

² The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

³ Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.

⁴ Study conducted in HIV-positive adult subjects.

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Amprenavir	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	See text below for discussion of interaction.		
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Efavirenz	600 QHS, 9 d	400/100 BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir	600 single dose ^b	400/100 BID, 10 d	11	See text below for discussion of interaction.		
Ketoconazole	200 single dose	400/100 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	300 QD, 10 d; 150 QD, 10 d	400/100 BID, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-O-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-O-desacetyl rifabutin ¹				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir	800 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

¹ Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.

* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.

N/A =not available.

Effect of KALETRA on other Protease Inhibitors (PIs): The pharmacokinetics of single-dose indinavir and saquinavir, and multiple-dose amprenavir obtained in healthy subjects after at least 10 days of KALETRA 400/100 mg BID were compared to historical data in HIV-infected subjects (refer to Table 2 for information on study design and doses). Because of the limitations in the study design and the use of comparisons between healthy and HIV infected subjects, it is not possible to recommend definitive dosing recommendations. However, based on these comparisons, amprenavir 750 mg BID and indinavir 600 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC, lower C_{max} , and higher C_{min} compared to their respective established clinical dosing regimens. Saquinavir 800 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC and higher C_{min} to its respective established clinical dosing regimen (no comparative information regarding C_{max}). The clinical significance of the lower C_{max} and higher C_{min} is unknown. Appropriate doses of amprenavir, indinavir and saquinavir in combination with KALETRA with respect to safety and efficacy have not been established (see **PRECAUTIONS** – Table 6).

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in a controlled study of KALETRA of 24 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration. At present, there are no results from controlled trials evaluating the effect of KALETRA on clinical progression of HIV.

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA BID + stavudine + lamivudine compared to nelfinavir TID + stavudine + lamivudine

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg BID) plus stavudine and lamivudine versus nelfinavir (750 mg TID) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm³ (range: 2 to 949 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/mL (range: 2.6 to 6.8 log₁₀ copies/mL).

The percent of patients with HIV RNA <400 copies/mL and outcomes of patients through 24 weeks are summarized in Figure 2 and Table 3, respectively.

Figure 2: Virologic Response Through 24 Weeks (Study 863)

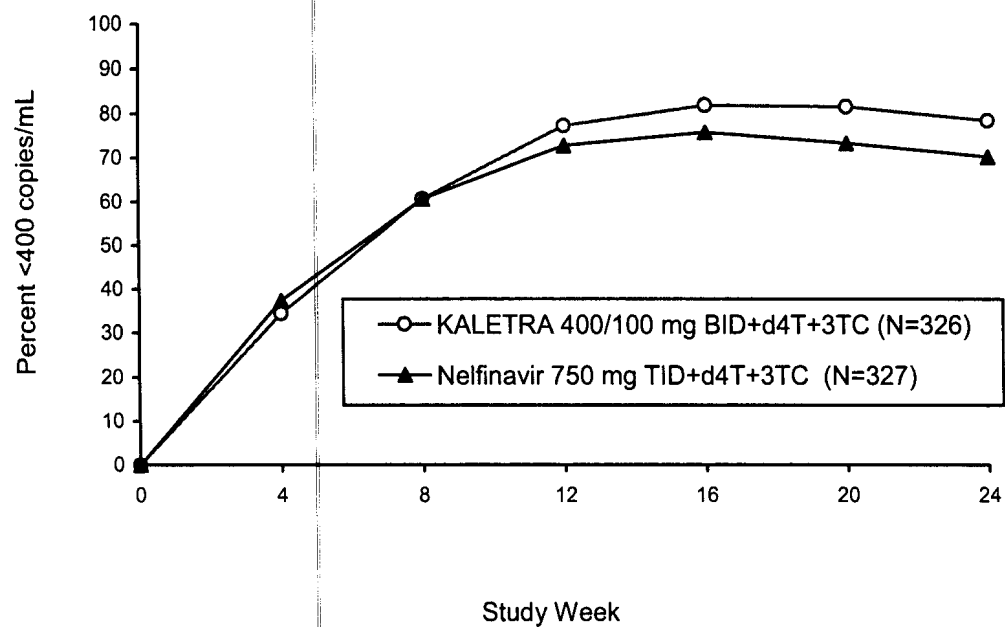


Table 3: Outcomes of Randomized Treatment Through Week 24 - (Study 863)

Outcome	KALETRA (400/100mg BID) + d4T + 3TC N=326	NELFINAVIR (750mg TID) + d4T + 3TC N=327
HIV RNA <400 copies/mL	79%	70%
HIV RNA >400 copies/mL	8%	16%
Discontinued due to KALETRA or nelfinavir adverse event*	2%	2%
Discontinued due to other adverse event*	2%	1%
Other**	8%	7%
Missing HIV RNA Level	2%	2%

*Includes laboratory abnormalities leading to discontinuation

**Lost to follow up, noncompliance, or consent withdrawn

In the KALETRA arm, the proportion <400 copies/mL for patients with baseline HIV RNA >100,000 copies/mL (78%) was similar to that for patients with baseline HIV RNA <100,000 copies/mL (81%).

Through 24 weeks of therapy, the proportion of patients with HIV RNA <50 copies/mL was 65% in the KALETRA arm and 60% in the nelfinavir arm.

Through 24 weeks of therapy, the mean increase from baseline in CD4 cell count was 154 cells/mm³ for the KALETRA arm and 150 cells/mm³ for the nelfinavir arm.

Four patients in the KALETRA arm and 6 patients in the nelfinavir arm experienced a new CDC Class C event following at least one week of treatment, including 3 patients in each arm who achieved HIV RNA <400 copies/mL at 24 weeks.

Study 720: KALETRA BID + stavudine + lamivudine

Study 720 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at three dose levels (Group I: 200/100 mg BID and 400/100 mg BID; Group II: 400/100 mg BID and 400/200 mg BID) plus lamivudine (150 mg BID) and stavudine (40 mg BID) in 100 patients. All patients were converted to open-label KALETRA at the 400/100 mg BID dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm³ (range: 3 to 918 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/mL (range: 3.3 to 6.3 log₁₀ copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 80% (78%) and the mean increase from baseline in CD4 cell count was 256 cells/mm³ for the 51 patients originally randomized to the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (13%) had discontinued the study for any reason. Four discontinuations (4%) were secondary to adverse events or laboratory abnormalities, and one of these discontinuations (1%) was attributed to a KALETRA adverse event.

Patients with Prior Antiretroviral Therapy

Study 765: KALETRA BID + nevirapine + NRTIs

Study 765 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at two dose levels (400/100 mg BID and 400/200 mg BID) plus nevirapine (200 mg BID) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40 years (range 22-66), were 73% Caucasian, and were 90% male. Mean baseline CD4 cell count was 372 cells/mm³ (range 72 to 807 cells/μL) and mean baseline plasma HIV-1 RNA was 4.0 log₁₀ copies/mL (range 2.9 to 5.8 log₁₀ copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 75% (58%) and the mean increase from baseline in CD4 cell count was 174 cells/mm³ for the 36 patients receiving the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (19%) had discontinued the study for any reason. Six discontinuations (9%) were secondary to adverse events or laboratory abnormalities, and three of these discontinuations (4%) were attributed to KALETRA adverse events.

CONTRAINDICATIONS

KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of KALETRA 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. These drugs are listed in Table 4.

Table 4: Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antiarrhythmics	Flecainide, Propafenone
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about drugs that should not be taken with KALETRA. This statement is included on the product’s bottle label.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics: Drug-Drug Interactions, CONTRAINDICATIONS – Table 4: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 5: Drugs That Should Not Be Co-administered With KALETRA and Table 6: Established and Other Potentially Significant Drug Interactions**).

Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for sildenafil.)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

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

Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS – Lipid Elevations**). 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 for recurrence during KALETRA 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 KALETRA 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 persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA 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.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see **MICROBIOLOGY**).

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 KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS** – Table 8). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at

periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS Table 6: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: **"ALERT: Find out about drugs that should NOT be taken with KALETRA."** A Patient Package Insert (PPI) for KALETRA is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients taking didanosine should take didanosine one hour before or two hours after KALETRA.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA 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 (see **Table 6: Established and Other Potentially Significant Drug Interactions**). 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 KALETRA.

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA 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.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with KALETRA are included in **Table 5: Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 5: Drugs That Should Not Be Co-administered With KALETRA

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 KALETRA 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 extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (<i>hypericum perforatum</i>)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 6: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
 (See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 1 and 2)

Concomitant Drug Class: Drug Name	Effect on Concentration of lopinavir or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ Lopinavir	A dose increase of KALETRA 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 patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see DOSAGE AND ADMINISTRATION). 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 KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (given with food).
HIV-Protease Inhibitors: amprenavir*, indinavir*, saquinavir*	↑ Amprenavir (Similar AUC, ↓ C _{max} , ↑ C _{min}) ↑ Indinavir (Similar AUC, ↓ C _{max} , ↑ C _{min}) ↑ Saquinavir (Similar AUC, ↑ C _{min})	Appropriate doses of the combination with respect to safety and efficacy have not been established (see CLINICAL PHARMACOLOGY : Table 2 and Effect of KALETRA on other Protease Inhibitors (PIs)).
HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
<i>Other Agents</i>		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, 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. KALETRA 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 dosage 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/day) are not recommended.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 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 of rifabutin may be necessary.
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Disulfiram/metronid- azole		KALETRA oral solution contains alcohol, which can produce 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 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*, cerivastatin	↑ Atorvastatin ↑ Cerivastatin	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.

* See CLINICAL PHARMACOLGY for Magnitude of Interaction, Tables 1 and 2

Other Drugs:

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

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

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

Pregnancy

Pregnancy Category C: No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m² or 300 mg lopinavir/75 mg ritonavir per m². Naive patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m² dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4 cell count was 838 cells/mm³ and mean baseline plasma HIV-1 RNA was 4.7 log₁₀ copies/mL.

Through 24 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/mL was 82% for antiretroviral naive patients and 66% for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 328

cells/mm³ for antiretroviral naïve and 335 cells/mm³ for antiretroviral experienced patients treated through 24 weeks. At 24 weeks, one patient (1%) had prematurely discontinued the study. This discontinuation was secondary to an HIV-related event in an antiretroviral experienced patient that was not attributed to a KALETRA adverse event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m² BID regimen without nevirapine and the 300/75 mg/m² BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

ADVERSE REACTIONS

Adults:

Treatment-Emergent Adverse Events: KALETRA has been studied in 612 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 2.8% in KALETRA and 3.1% in nelfinavir treated patients in Study 863.

Drug related clinical adverse events of moderate or severe intensity in ≥ 2% of patients treated with combination therapy including KALETRA for up to 24 weeks (Phase III) and for up to 72 weeks (Phase I/II) are presented in Table 7. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS**.

Table 7: Percentage of Patients with Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Patients

	Antiretroviral Naïve Patients			Protease Inhibitor Experienced Patients
	Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
	KALETRA 400/100 mg TID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID ² + d4T + 3TC (N= 84)	KALETRA BID ³ + nevirapine + NRTIs (N= 186)
Body as a Whole				
Abdominal Pain	3.1%	2.4%	4.8%	1.1%
Asthenia	3.4%	2.8%	7.1%	5.4%
Headache	2.5%	1.8%	7.1%	1.6%
Pain	0.3%	0.0%	2.4%	1.6%
Digestive System				
Abnormal Stools	0.0%	0.3%	6.0%	1.6%
Diarrhea	13.8%	14.4%	23.8%	15.1%
Nausea	6.4%	4.0%	15.5%	2.2%
Vomiting	2.1%	2.4%	4.8%	1.6%
Nervous System				
Insomnia	1.5%	1.2%	2.4%	1.1%
Skin and Appendages				
Rash	0.6%	1.2%	3.6%	2.0%

¹ Includes adverse events of possible, probable or unknown relationship to study drug.
² Includes adverse event data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35]) and 400/200 mg BID [N=36]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.
³ Includes adverse event data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.

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

Body as a Whole: Back pain, chest pain, chest pain substernal, chills, drug interaction, drug level increased, face edema, fever, flu syndrome, malaise, and viral infection.

Cardiovascular System: Deep vein thrombosis, hypertension, palpitation, thrombophlebitis, and vasculitis.

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

Endocrine System: Cushing's syndrome 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, and weight loss.

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

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

Respiratory System: Bronchitis, dyspnea, lung edema, and sinusitis.

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

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

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

Laboratory Abnormalities: The percentages of adult patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 8.

Table 8: Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Patients

Variable	Limit ¹	Antiretroviral Naive Patients			Antiretroviral Experienced Patients
		Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
		KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID ² + d4T + 3TC (N=84)	KALETRA BID ³ + NNRTI + NRTIs (N=186)
Chemistry	High				
Glucose	>250 mg/dL	1.6%	0.6%	2.4%	4.4%
Uric Acid	>12 mg/dL	1.3%	0.3%	3.6%	0.5%
SGOT/AST	>180 U/L	0.3%	2.2%	9.5%	4.4%
SGPT/ALT	>215 U/L	1.0%	2.2%	8.3%	6.6%
GGT	>300 U/L	N/A	N/A	3.6%	24.6% ⁴
Total Cholesterol	>300 mg/dL	6.7%	2.8%	14.3%	25.7%
Triglycerides	>750 mg/dL	5.1%	0.9%	10.7%	26.2%
Amylase	>2 x ULN	1.9%	1.9%	4.8%	3.3%

Chemistry	Low				
Inorganic Phosphorus	<1.5 mg/dL	0.0%	0.0%	0.0%	2.2%
Hematology	Low				
Neutrophils	$0.75 \times 10^9/L$	0.6%	1.6%	2.4%	2.7%

- ¹ ULN = upper limit of the normal range; N/A = Not Applicable.
² Includes clinical laboratory data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=36]).
³ Includes clinical laboratory data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.
⁴ GGT was only measured in 69 patients receiving 400/100 mg BID or 400/200 mg BID in combination with nevirapine.

Pediatrics:

Treatment-Emergent Adverse Events: KALETRA has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Rash (2%) was the only drug-related clinical adverse event of moderate or severe intensity in $\geq 2\%$ of pediatric patients treated with combination therapy including KALETRA (300/75 mg/m²) for up to 24 weeks (Study 940). This includes adverse events of at least possible, probable or unknown relationship to study drug.

Laboratory Abnormalities: The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ Pediatric Patients

Variable	Limit ¹	KALETRA BID ² + RTIs (N=100)
Chemistry	High	
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	7.0%
SGPT/ALT	>215 U/L	4.0%
Total cholesterol	> 300 mg/dL	2.0%
Amylase	> 2.5 x ULN	4.0%
Chemistry	Low	
Sodium	< 130 mEq/L	3.0%
Hematology	Low	
Platelet Count	< $50 \times 10^9/L$	4.0%
Neutrophils	< $0.40 \times 10^9/L$	2.0%

- ¹ ULN = upper limit of the normal range.
² Includes clinical laboratory data from the 230/57.5 mg per m² (N=49) and 300/75 mg per m² (N=51) dose arms.

OVERDOSAGE

KALETRA 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 KALETRA is limited. Treatment of overdose with KALETRA 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 KALETRA. 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 KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of KALETRA is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA 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) (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS – Table 6**).

Pediatric Patients

In children 6 months to 12 years of age, the recommended dosage of KALETRA 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. The following table contains dosing guidelines for KALETRA oral solution based on body weight.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
<u>Without nevirapine or efavirenz</u>		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		2.5 mL
>25 to 30 kg		3.0 mL
>30 to 40 kg		3.5 mL
>40 kg	Adult dose	5 mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15 to 50 kg (approximately equivalent to 300/75 mg/m²) twice daily taken with food, up to a maximum dose of 533/133 mg in children >50 kg twice daily should be considered 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). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS – Table 6**).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
-------------	---------------	--

<u>With nevirapine or efavirenz</u>		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
>10 to <15 kg		2.0 mL
15 to 50 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 40 kg		4.5 mL
>40 to 50 kg		5.0 mL (or 3 capsules)
>50 kg	Adult dose	6.5 mL (or 4 capsules)

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

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

HOW SUPPLIED

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the corporate logo  and the Abbo-Code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules in the following package sizes:

Bottles of 180 capsules each..... (NDC 0074-3959-77)

Packages of 120 unit dose blisters.....(NDC 0074-3959-11)

Recommended storage: Store KALETRA soft gelatin capsules at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:

160 mL bottle.....(NDC 0074-3956-46)

Recommended storage: Store KALETRA oral solution at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, 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), oral solution should be used within 2 months.

Revised: NEW

ABBOTT  LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

----- (Perforation) -----

KALETRA™
(lopinavir/ritonavir) capsules

Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

Additional copies are available from:

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Division of Drug Information, HFD-240
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(Tel) 301-827-4573

(Internet) [Http://www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm)

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**December 2002
BP**

Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

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Guidance For Industry¹

Food-Effect Bioavailability and Fed Bioequivalence Studies

This guidance represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance provides recommendations to sponsors and/or applicants planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug products as part of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications. This guidance applies to both immediate-release and modified-release drug products. The guidance addresses how to meet the BA and BE requirements in 21 CFR 320, 314.50 (d) (3), and 314.94 (a) (7) as they apply to oral dosage forms. This guidance provides recommendations for food-effect BA and fed BE study designs, data analysis, and product labeling. It also provides information on when food-effect BA and fed BE studies should be performed.²

II. BACKGROUND

Food effect BA studies are usually conducted for new drugs and drug products during the IND period to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Fed BE studies, on the other hand, are conducted for ANDAs to demonstrate their bioequivalence to the reference listed drug (RLD) under fed conditions.

A. Potential Mechanisms of Food Effects on BA

¹ This guidance has been prepared by the Food Effect Working Group of the Biopharmaceutics Coordinating Committee in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

² See also the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products • General Considerations*.

Food can change the BA of a drug and can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by various means, including

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. We recommend use of high-calorie and high-fat meals during food-effect BA and fed BE studies.

B. Food Effects on Drug Products

Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution.³ However, for some drugs in this class, food can influence BA when there is a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. For rapidly dissolving formulations of BCS Class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. However, we expect the food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products (BCS Class II, III, and IV) and for all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

³ See the guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

III. RECOMMENDATIONS FOR FOOD-EFFECT BA AND FED BE STUDIES

This section of the guidance provides recommendations on when food-effect BA studies should be conducted as part of INDs and NDAs and when fed BE studies should be conducted as part of ANDAs. For postapproval changes in an approved immediate- or modified-release drug product that requires in vivo redocumentation of BE under fasting conditions, fed BE studies are generally unnecessary.

A. Immediate-Release Drug Products

1. *INDs/NDAs*

We recommend that a food-effect BA study be conducted for all new chemical entities (NCEs) during the IND period.

Food-effect BA studies should be conducted early in the drug development process to guide and select formulations for further development. Food-effect BA information should be available to design clinical safety and efficacy studies and to provide information for the CLINICAL PHARMACOLOGY and/or DOSAGE AND ADMINISTRATION sections of product labels. If a sponsor makes changes in components, composition, and/or method of manufacture in the clinical trial formulation prior to approval, BE should be demonstrated between the to-be-marketed formulation and the clinical trial formulation.

Sponsors may wish to use relevant principles described in the guidance for industry on *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC-IR guidance) to determine if in vivo BE studies are recommended. These BE studies, if indicated, should generally be conducted under fasting conditions.

2. *ANDAs*

In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I) (see footnote 3), or
- When the DOSAGE AND ADMINISTRATION section of the RLD label states that the product should be taken only on an empty stomach, or

- When the RLD label does not make any statements about the effect of food on absorption or administration.

B. Modified-Release Drug Products

We recommend that food-effect BA and fed BE studies be performed for all modified-release dosage forms.

1. INDs/NDAs

We recommend a study comparing the BA under fasting and fed conditions for all orally administered modified-release drug products.

When changes occur in components, composition, and/or method of manufacture between the to-be-marketed formulation and the primary clinical trial material, the sponsor may wish to use relevant principles described in the guidance for industry on *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls: In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (SUPAC-MR guidance) to determine if documentation of in vivo BE is recommended. These BE studies, if indicated, should generally be conducted under fasting conditions.

2. ANDAs

In addition to a BE study under fasting conditions, a BE study under fed conditions should be conducted for all orally administered modified-release drug products.

IV. STUDY CONSIDERATIONS

This section provides general considerations for designing food effect BA and fed BE studies. A sponsor may propose alternative study designs and data analyses. The scientific rationale and justification for these study designs and analyses should be provided in the study protocol. Sponsors may choose to conduct additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g. different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that co-administration with food can result in *dose dumping*, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects.

A. General Design

We recommend a randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design for studying the effects of food on the BA of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and following a test meal

(fed condition) in the other period. We recommend a similar, two-treatment, two-period, two-sequence crossover design for a fed BE study except that the treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BA and fed BE studies.

B. Subject Selection

Both food-effect BA and fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on BA to claim an absence of food effects, or to claim BE in a fed BE study (see DATA ANALYSIS AND LABELING section). A minimum of 12 subjects should complete the food-effect BA and fed BE studies.

C. Dosage Strength

In general, the highest strength of a drug product intended to be marketed should be tested in food-effect BA and fed BE studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For ANDAs, the same lot and strength used in the fasting BE study should be tested in the fed BE study. For products with multiple strengths in ANDAs, if a fed BE study has been performed on the highest strength, BE determination of one or more lower strengths can be waived based on dissolution profile comparisons (for details see the guidance on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*).

D. Test Meal

We recommend that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.⁴ The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference. In NDAs, it is recognized that a sponsor can choose to conduct food-effect BA studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal described above.

⁴ An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

E. Administration

Fasted Treatments: Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

F. Sample Collection

For both fasted and fed treatment periods, timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites, and sponsors should refer to the guidance on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* for recommendations on these issues. Consideration should be given to the possibility that co-administration of a dosage form with food can alter the time course of plasma drug concentrations so that fasted and fed treatments can have different sample collection times.

V. DATA ANALYSIS AND LABELING

Food-effect BA studies may be exploratory and descriptive, or a sponsor may want to use a food-effect BA study to make a label claim.⁵ The following exposure measures and pharmacokinetic parameters should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- Total exposure, or area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-t})
- Peak exposure (C_{max})
- Time to peak exposure (T_{max})
- Lag-time (t_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant pharmacokinetic parameters

Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported. An equivalence approach is

⁵ Regulations on labeling requirements for a drug product submitted in an NDA can be found in 21 CFR part 201.

recommended for food-effect BA (to make a claim of no food effects) and fed BE studies, analyzing data using an average criterion. Log-transformation of exposure measurements (AUC and C_{max}) prior to analysis is recommended. The 90 percent CI for the ratio of population geometric means between test and reference products should be provided for AUC_{0-inf} , AUC_{0-t} , and C_{max} (see guidance for industry on *Statistical Approaches to Establishing Bioequivalence*). For IND or NDA food-effect BA studies, the fasted treatment serves as the reference. For ANDA fed BE studies, the RLD administered under fed condition serves as the reference treatment.

The effect of food on the absorption and BA of a drug product should be described in the CLINICAL PHARMACOLOGY section of the labeling. In addition, the DOSAGE AND ADMINISTRATION section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance (i.e., whether or not the changes in systemic exposure caused by co-administration with food results in safety or efficacy concerns, or when there is no important change in systemic exposure but there is a possibility that the drug substance causes GI irritation when taken without food).

For an NDA, an absence of food effect on BA is not established if the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80-125 percent for either AUC_{0-inf} (AUC_{0-t} when appropriate) or C_{max} . When the 90 percent CI fails to meet the limits of 80-125 percent, the sponsor should provide specific recommendations on the clinical significance of the food effect based on what is known from the total clinical database about dose-response (exposure-response) and/or pharmacokinetic-pharmacodynamic relationships of the drug under study. The clinical relevance of any difference in T_{max} and t_{lag} should also be indicated by the sponsor. The results of the food-effect BA study should be reported factually in the CLINICAL PHARMACOLOGY section of the labeling and should form the basis for making label recommendations (e.g., *take only on an empty stomach*) in the DOSAGE AND ADMINISTRATION section of the labeling. The following are examples of language for the package insert:

A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased 57% and 45%, respectively, under fed conditions. This increase in exposure can be clinically significant, and therefore [the drug] should be taken only on an empty stomach (1 hour before or 2 hours after a meal)

A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 15% while the AUC remained unchanged. This decrease in exposure is not clinically significant, and therefore [the drug] could be taken without regards to meals.

An absence of food effect on BA is indicated when the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is contained in the equivalence limits of 80-125 percent for AUC_{0-inf} (AUC_{0-t} when appropriate) and C_{max} . In this case, a sponsor can make a specific claim in the CLINICAL PHARMACOLOGY or DOSAGE AND ADMINISTRATION section of the label that no food effect on BA is expected

provided that the $T_{\max}$ differences between the fasted and fed treatments are not clinically relevant. The following is an example of language for the package insert:

The $C_{\max}$ and AUC data from a food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. Therefore, [the drug product] may be taken without regard to meals.

For an ANDA, BE of a test product to the RLD product under fed conditions is concluded when the 90 percent CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80-125 percent for AUC and $C_{\max}$. Although no criterion applies to $T_{\max}$, the $T_{\max}$ values for the test and reference products are expected to be comparable based on clinical relevance. The conclusion of BE under fed conditions indicates that with regard to food, the language in the package insert of the test product can be the same as the reference product.

VI. OTHER CONSIDERATIONS

A. Sprinkles

In NDAs, the labeling of certain drug products (e.g., controlled-release capsules containing beads) can recommend that the product be sprinkled on soft foods, such as applesauce, and swallowed without chewing. For the labeling to indicate that the drug product can be sprinkled on soft foods, additional in vivo relative BA studies should be performed by sprinkling the product on the soft foods to be listed in the labeling (test treatment) and comparing it to the product administered in the intact form (reference treatment), then administering both on an empty stomach.

In ANDAs, BE of the test to the RLD is demonstrated in a single dose crossover study. Both treatments should be sprinkled on one of the soft foods mentioned in the labeling, usually applesauce. The BE data should be analyzed using average BE and the 90 percent CI criteria should be used to declare BE. If there are questions about other foods, the design, or the analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.

B. Special Vehicles

For NDAs, the labeling for certain oral solution products (e.g., cyclosporine oral solution, modified) recommends that the solution be mixed with a beverage prior to administration. The BA of these products can change when mixed with different beverages due to the formation of complex mixtures and other physical-chemical and/or physiological factors. NDA sponsors should contact the Office of Clinical Pharmacology and Biopharmaceutics to determine what data should be submitted to support labeling.

In ANDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be mixed with one of the beverages mentioned in the labeling. Sponsors

should provide evidence that BE differences would not be expected from the use of other listed vehicles. The BE data should be analyzed using average BE, and the 90 percent CI criteria should be used to declare BE. If there are questions about other vehicles, or the design or analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.



Review article

Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system

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Received 29 January 2004; accepted in revised form 5 February 2004

Available online 12 April 2004

Abstract

Since its inception in 1995, the biopharmaceutical classification system (BCS) has become an increasingly important tool for regulation of drug products world-wide. Until now, application of the BCS has been partially hindered by the lack of a freely available and accurate database summarising solubility and permeability characteristics of drug substances. In this report, orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain. Of the 130 orally administered drugs on the WHO list, 61 could be classified with certainty. Twenty-one (84%) of these belong to class I (highly soluble, highly permeable), 10 (17%) to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). A further 28 drugs could be provisionally assigned, while for 41 drugs insufficient or conflicting data precluded assignment to a specific BCS class. A total of 32 class I drugs (either certain or provisional classification) were identified. These drugs can be further considered for biowaiver status (drug product approval based on dissolution tests rather than bioequivalence studies in humans).

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Keywords: Biopharmaceutical classification system; Permeability; Solubility; Absorption; World Health Organization; Essential Medicines

1. Introduction

Since the biopharmaceutics classification system (BCS) was introduced in 1995, it has had an increasing impact on regulatory practice. The BCS presented a new paradigm in bioequivalence, based on scientific principles. According to the tenets of the BCS, certain drug products can be considered for biowaivers, i.e. approving the product based on in vitro dissolution tests rather than requiring bioequivalence studies in human subjects. At first, biowaivers were only applied to Scale-Up and Postapproval Changes (SUPAC), but later the biowaiver principle was extended to the approval of new generic drug products. As a result, unnecessary human experiments can be avoided and the costs of developing generic products can be significantly lowered.

To classify a drug according to the BCS, the solubility, dose and permeability of the drug must be known. According to the FDA guidance for the industry 'Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system' (August 2000), a biowaiver can currently be requested only for solid, orally administered immediate-release products (>85% release in 30 min), containing drugs with a high solubility over the pH range from 1 to 7.5 (dose/solubility ($D:S$) ratio <250 ml) and a high permeability (fraction absorbed >90%). In addition, only excipients which do not affect the rate or extent of absorption may be used. Further restrictions are that drugs with a narrow therapeutic range and drug products designed to be absorbed in the oral cavity may not be considered for biowaivers.

The possibility of considering biowaivers for drugs assigned to BCS classes other than class I (high solubility/high permeability) is currently being discussed.

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Thus, the effect of the BCS on regulatory practices is likely to increase even more in the future.

The aim of this work was to search the public domain for all solubility and permeability data relevant to orally administered drugs belonging to the WHO model list of Essential Medicines. According to the quality and consistency of the data, drugs were then assigned to a BCS class (as defined by the FDA), given a provisional assignment or it was determined that data were too inconclusive to assign the drug to a specific BCS class.

2. Materials and methods

The basis for this study was the Essential Medicines WHO Model List, Core List, 12th edition (revised April 2002). The newest edition of the WHO list can be downloaded from the following website: <http://www.who.int/medicines/organization/par/edl/eml.shtml>. Research on the solubility and permeability of the drugs on the list that are orally administered was carried out using PubMed Central, the general pharmaceutical literature and information obtained from pharmaceutical firms and authorities. All of this information was freely available on the Internet or from other sources. The search in the PubMed Central was conducted using the following keywords in different combinations: absolute, absorption, aqueous, bioavailability, permeability, pharmacokinetics, solubility and the name of the drug.

Whenever possible, original literature was consulted in order to evaluate the quality of the data and to make the classification as transparent as possible. Data from secondary sources were included for completeness or when original literature could not be located.

All guidelines of the FDA, including the one for classification of drugs in the BCS, can be found at the following website: <http://www.fda.gov/cder/guidance/>. The three parameters needed for classification of drugs according to BCS are the dose, the solubility and the permeability.

According to the biowaiver guidance (August 2000), high solubility drugs are those with a ($D:S$) ratio of <250 ml over the range of pH 1.0–7.5 at 37 °C. The FDA biowaiver guidance states further, that in the absence of evidence suggesting instability in the GI-tract, a drug substance is considered highly permeable when the extent of absorption (as measured by fraction of dose absorbed, rather than systemic bioavailability) in humans is determined to be 90% or more of an administered dose.

The three individual parameters were evaluated as follows.

2.1. Dose

The dose used for calculation of $D:S$ ratio was the highest recommended dose (in mg) stated in the WHO list for that drug. This dose may differ from specifications given

in prescribing information, resulting in a different ($D:S$) ratio for some drugs in some countries.

2.2. Solubility

Data for the solubility (in mg/ml) over the entire range pH value 1–7.5 at 37 °C were located whenever possible. In some cases, where only limited solubility data were available (e.g. solubility at just one pH value in this range), it was nonetheless clear that the solubility was too low at at least one relevant pH condition for the drug to fall into the 'highly soluble' category. In some cases, the pH-dependency of the solubility was determined by Prof. Dressman's group at the University of Frankfurt and collaborators at Hoffmann-La Roche and Merck KGaA. The solubility experiments at the University of Frankfurt were carried out for aciclovir, allopurinol, aspirin, carbamazepine, chloroquine phosphate, doxycycline, diazepam, erythromycin, ibuprofen, mebendazole, metronidazole, potassium phenoxymethylpenicillin and rifampicin using the saturation shake-flask method. The solubility of saquinavir was determined with a similar method at Hoffmann-La Roche. The values for albendazole, glibenclamide, griseofulvin, levothyroxine T4, niclosamide and phenytoin were determined at Merck KGaA. These solubility experiments were typically conducted over 24 h at 37 °C in buffers at pH values of 1.2, 4.5 and 6.8 and in deionised water. In all cases, the samples were analysed by UV-spectroscopy or HPLC and values were determined in triplicate.

Dividing the dose (mg) by the solubility (mg/ml) yields a ratio with volumetric units (ml). This $D:S$ ratio is then compared with the FDA criterion of 250 ml to establish whether the drug is highly soluble or not.

2.3. Permeability

For permeability determinations the FDA prefers pharmacokinetic data in humans, human perfusion data, data from in vivo or in situ animal models or results in validated cell-culture monolayers [1]. To date, computational methods (e.g. based on polar surface area or log P of the molecule) have not been accepted by the FDA as sufficiently reliable for this purpose.

In this work, fraction absorbed data in human studies was the primary source for permeability data. In some cases where data from Caco-2 cells experiments as well as in humans were available (cimetidine, ciprofloxacin, furosemide, phenoxymethylpenicillin, phenytoin and propranolol), these were also taken into consideration as additional evidence. In a few exceptional cases, animal data was also utilised (acetazolamide, benznidazole, furosemide, sulfadiazine).

Data in humans was taken from papers using the following experimental designs:

- Oral vs. i.v. application,
- urinary recovery,
- radioactive-labelled drugs, or
- human perfusion studies.

The fraction absorbed was located if possible, otherwise the absolute bioavailability was recorded. In some cases, it was apparent that the bioavailability of the drug was compromised by degradation in the GI-tract or due to a first-pass effect. These drugs are marked with an asterisk in the tables.

For poorly soluble drugs, it was not always possible to determine whether bioavailabilities of <90% were due exclusively to solubility problems or whether poor permeability characteristics also played a role. In some cases, the higher bioavailability of the drug when administered with food was taken as an indication that the reason for <90% absorption in the fasted state was primarily a solubility problem rather than a permeability problem [2].

On the basis of these data, the drugs were then classified according to the guidelines given in the FDA biowaiver guidance [1].

3. Results

For better comprehension, the list has been divided in three parts.

3.1. Drugs with reliable solubility and permeability data

Table 1 includes all drugs with sufficient data for both solubility and permeability to predict the BCS classification with certainty. Sixty-four of the 130 drugs (49%) of the WHO 'Essential drug list' could be assigned to a specific BCS class with certainty.

3.2. Drugs for which complete solubility and/or permeability data are lacking

Table 2 contains drugs for which either the solubility or permeability data (or both) were not completely satisfactory. For example, if specific solubility data in the required pH range could not be found or if bioavailability data were only available from a secondary source. Also, in some cases, the type of data generated was not appropriate for a definitive classification (e.g. urinary excretion data from oral administration without i.v. comparison). In all cases, however, it was possible to provisionally assign the drug to a specific BCS class. Twenty-five of the drugs (20%) could be provisionally assigned to one of the BCS classes.

3.3. Drugs with inconclusive data

Table 3 includes drugs which could not be assigned to a specific BCS class based on the data available, e.g. class II/

IV drugs where bioavailability was <90%, but the low bioavailability could be the result of either low solubility or poor permeability or both. Another case would be contradictory data from different sources (e.g. for the solubility of verapamil).

For drugs shown in Table 3, we found conflicting or insufficient data for either solubility or permeability or both. Assignment to a specific BCS class was not possible, but the decision could be narrowed to one of two classes. This was the case for 41 (32%) of the orally administered drugs on the WHO list.

4. Discussion

As stated in Section 1, assignment of a drug to a particular BCS class is an important parameter for biopharmaceutical questions. The availability of high quality data for solubility and permeability is very important to avoid wrong classifications and wasting resources on performing unnecessary human studies to establish bioequivalence. Finding suitable information about solubility and permeability data proved to be a lot more cumbersome than expected. The authors of most articles reviewed here did not, of course, have the suitability of their articles for BCS classification in mind at the time of writing, so a good deal of the data is only partially helpful.

4.1. Dose

According to the FDA biowaiver guidance, the highest dose administered must be used to determine the ($D:S$) ratio in the BCS. For the classifications in our tables, we used the highest doses recommended in the WHO list. This recommendation may differ from the one given by the manufacturers. For example, in the case of aspirin, the WHO list indicates a range of 100–500 mg as a single dose, but in German prescribing information values of up to 1000 mg are found. Obviously, the choice of the maximum recommended dose has an impact on the calculation of the $D:S$ ratio and, for some drugs, may shift the classification from 'highly' soluble to 'not highly' soluble.

4.2. Solubility

To our knowledge no database available in the public domain with solubility data suitably reported for BCS purposes exist. The data found in articles usually consists of data measured at 25 °C and often at only one pH-value. As the FDA guidance demands that the solubility of a drug has to be determined at 37 °C over the pH range 1–7.5, the information found is therefore often not sufficient for a conclusive classification. This applies particularly to ionisable drugs whose solubility can change dramatically depending on pH. Further, it was not always clear whether

Table 1
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: *Drugs with reliable solubility and permeability data*

Drug	Solubility	Permeability	Dose (mg)	BCS class ^a	References
Abacavir antiretroviral	High	Low	300 (sulfate)	III	[4–7]
Acetylsalicylic acid pain relief	High	Low	100–500	III*/**	[8–18]
Aciclovir antiviral	High	Low	200	III	[12,19–25]
Allopurinol gout	High	Low	100	III	[12,16,25–31]
Aluminium hydroxide gastro-intestinal agent	Low	Low	500	IV	[30,32–34]
Amiloride diuretic	High	High	5 (hydrochloride)	I	[12,16,30,35,36]
Ascorbic acid vitamin	High	Low	50 (– 1000)	III*	[12,16,37]
Atenolol B-blocker	High	Low	50; 100	III	[1,12,16,38–42]
Captopril antihypertensive	High	Low	25	III	[12,16,43,44]
Carbamazepin antiepileptic	Low	High	100; 200	II	[1,25,45,46]
Chloramphenicol antibiotic	High	Low	250	III	[12,16,47,48]
Chloroquine antimalarial agent	High	High	100 (Phosphate) 150 (Sulfate)	I	[12,23,25,49]
Cimetidine H2-receptor antagonist	High	Low	200	III	[12,16,38,50–56]
Sodium Cloxacillin antibiotic	High	Low	500; 1000 (Na-salz)	III	[12,16,57,58]
Codeine phosphate antitussive/analgetic	High	Low	30	III	[12,16,59,60]
Colchicine antigout agent	High	Low	0.5	III	[12,61–63]
Cyclophosphamide antineoplastic	High	High	25	I	[12,64–66]
Dapsone antirheumatic/leprosy	Low	High	25; 50; 100	II	[12,16,23,30,67,68]
Diazepam Benzodiazepine	High	High	2; 5	I	[12,16,25,69–72]
Digoxine cardiac glycoside	High	High	0.625; 0.25	I*	[69,73–81]
Doxycycline antibiotic	High	High	100 (Hydrochlorid)	I	[12,23,25,82]
Ergotamine Tartrate migraine	High	Low	1 (tartrate)	III*	[12,16,83–86]
Fluconazole antifungal	High	High	50	I	[16,91–95]
Furosemide diuretic	Low	Low	40	IV*	[12,38,42,56,70,96–102]
Griseofulvin antifungal	Low	High	125; 250	II	[25,79,103–105]
Hydralazine antihypertensive	High	Low	25; 50 (hydrochloride)	III*	[4,12,16,106,107]
Hydrochlorothiazide diuretic	High	Low	25	III	[1,12,16,23,30,102]
Ibuprofen pain relief	Low	High	200; 400	II	[12,25,108–110]
Indinavir antiviral	Low	Low	200; 300; 400 (Sulfat)	IV*	[4,16,30,111–113,284]
Levodopa + (Carbidopa) Parkinson's disease	High	High	100 + 10; 250 + 25	I*	[12,16,30,42,114,115]
Levonorgestrel hormone	High	High	0.15 (+ 0.03 Ethinylestradiol) 0.25 (+ 0.05 Ethinylestradiol) 0.75 (pack of two) + D43	I	[12,16,116,117]
Levothyroxine thyroid	High	Low	0.05; 0.1 (Sodium salt)	III	[12,25,118–120]
Metformine antidiabetic	High	Low	500 (hydrochloride)	III*	[12,16,38,121–123]
Methyldopa antihypertensive	High	Low	250	III*/**	[1,12,30,124,125]
Metronidazole antibiotic	High	High	200–500	I	[12,25,126–128]
Nelfinavir antiviral	Low	Low	250 (mesilate)	IV*	[30,33,112,129,284]
Nifedipine Ca-channel blocker	Low	High	10	II*	[12,16,38,130–132]
Nitrofurantoin antibacterial	Low	High	100	II	[12,16,30,133]
Paracetamol (Acetaminophen) pain relief	High	Low	100–500	III*	[12,16,38,69,134–137]
Penicillamine Chron. Polyarthritits	High	Low	250	III	[12,16,138–140]
Phenobarbital barbiturate	High	High	15–100	I	[12,16,23,30,141]
Phenoxy-methylpenicillin antibiotic	High	High	250 (Potassium salt)	I	[12,25,142,143]
Phenytoin antiepileptic	Low	High	25; 50; 100	II	[12,23,25,56,144–146]
Prednisolone glucocorticoid	High	High	5	I	[16,69,147–149]
Primaquine antimalarial	High	High	7.5; 15 (diphosphate)	I	[12,150]
Promethazine antihistamine	High	Low	10; 25 (hydrochloride)	III*	[12,16,151,152]
Propranolol B-blocker	High	High	20; 40 (hydrochloride)	I*	[1,12,38,153–155]
Propylthiouracil cystostatic	High	Low	50	III	[12,16,30,156,157]
Pyrazinamide tuberculosis	High	High	400	I	[12,16,158]
Pyridostigmine Myasthenia gravis	High	Low	60 (bromide)	III	[12,159–161]
Riboflavin vitamin	High	High	5	I*	[12,16,162]
Ritonavir antiviral	Low	Low	100	IV*	[4,165,284]
Salbutamol B-sympathomimetic	High	High	4 (sulfate)	I*	[12,166–168]
Saquinavir antiviral	Low	Low	200, available as mesylate (hard gelatine capsule) or as free base (soft gelatine capsule)	IV (mesylate)/IV (free base)*	[25,30,33,112,169,284]
Stavudine antiviral	High	High	15; 20; 30; 40	I	[170–172]
Sulfamethoxazole antibiotic	Low	High	100; 400	II	[12,16,173–175]

(continued on next page)

Table 1 (continued)

Drug	Solubility	Permeability	Dose (mg)	BCS class ^a	References
<i>Theophylline antiasthmatic</i>	<i>High</i>	<i>High</i>	100; 200; 300	<i>I</i>	[1,12,16,176–178]
Thiamine vitamin	High	Low	50 (hydrochloride)	III [#]	[12,16,33,179]
Trimethoprim antibiotic	Low	High	100; 200	II	[12,16,173–175]
Valproic acid antiepileptic	Low	High	200; 500 (sodium salt)	II	[12,16,23,180]
<i>Zidovudine antiviral</i>	<i>High</i>	<i>High</i>	300 (tablet); 100; 250 (capsule)	<i>I*</i>	[7,12,16,21,181,182]

^a Italics denotes class I drugs according to the FDA criteria; bold text denotes class III drugs with permeabilities corresponding to at least 80% absorption.
* First pass effect; ** Degradation in the GI-Tract; # active transport.

the experiment was done in a buffer solution or if the pH was only adjusted with acid or base, and if the pH was checked before and after the experiment was conducted. Moreover, the comparison of different experiments is often difficult because of a lack of standard deviation values and statistical calculations. Some articles, however, did provide appropriate data for the BCS classification, e.g. where the intrinsic solubility of drugs (where the solubility is the lowest) was provided. If this intrinsic solubility lies between pH 1 and 7.5, the classification of the solubility of the drug can be made with the help of its pK_a and the Hendersson–Hasselbalch equation.

4.3. Permeability

Permeability data from humans is also not easy to find. As with solubility data, a database with freely available, reliable permeability data useful for BCS purposes was not found. The most common type of studies found were bioavailability studies. Since first-pass effects, degradation in the intestine and solubility-limited absorption can all influence the bioavailability, these studies can usually give at most a general indication of the permeability of the drug. The best and safest way to classify a drug as highly permeable is an absolute bioavailability study with a

Table 2
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: *Drugs for which complete solubility and/or permeability data are lacking*

Drug	Solubility	Permeability	Dose (mg)	BCS class ^a	References
Acetazolamide diuretic	Low	Low	250	IV	[16,183]
<i>Amoxicillin antibiotic</i>	<i>High</i>	<i>High</i>	250; 500 (anhydrous)	<i>I[#]</i>	[1,12,16,23,30,36]
Azathioprine immunosuppressive	Low	Low	50	IV	[12,16,23,184]
<i>Benznidazole antiprotozoal agent</i>	<i>High</i>	<i>High</i>	100	<i>I</i>	[30,185]
Biperiden antimuscarinic agent	High	Low	2 (hydrochloride)	III*	[12,186]
Didanosine antiviral	High	Low	25; 50; 100; 150; 200 (buff. chew., disp tablet)	III**	[16,21,187–189]
<i>Diethylcarbamazine anthelmintic</i>	<i>High</i>	<i>High</i>	50; 100 (Citrat)	<i>I</i>	[12,165]
<i>DL-Methionine chelating agent antidote</i>	<i>High</i>	<i>High</i>	250	<i>I[#]</i>	[12,30,33]
Ergocalciferol vitamin	High	Low	1.25	III	[12,33]
Ergometrine postpartum haemorrhage	High	Low	0.2 (hydrogen maleate)	III	[12,190,191]
Erythromycin antibiotic	High	Low	250 (Stearat od. Ethylsuccinat)	III*/**	[12,25,33,87–90]
Ethambutol hydrochloride tuberculosis	High	Low	100–400 (Hydrochlorid)	III	[12,16,23,33]
<i>Ethosuximide antiepileptic</i>	<i>High</i>	<i>High</i>	250	<i>I</i>	[12,23,192,193]
Iopanoic acid contrast medium	Low	High	500	II	[12,16,30]
<i>Isoniazid tuberculosis</i>	<i>High</i>	<i>High</i>	100–300	<i>I*</i>	[12,16,23,194]
<i>Lithium carbonate antidepressant</i>	<i>High</i>	<i>High</i>	300	<i>I</i>	[12,16,23,30]
Methotrexate antirheumatic/antineoplastic	High	Low	2.5 (sodium salt)	III [#]	[12,195–198]
Nalidixic acid antibacterial agent	Low	High	250; 500	II	[12,30]
Neostigmine Myasthenia gravis	High	Low	15 (bromide)	III	[12,23,160]
Nevirapine antiviral	Low	High	200	II	[30,199]
<i>Nicotinamide vitamin</i>	<i>High</i>	<i>High</i>	50	<i>I</i>	[12,16,33]
Nifurtimox antiprotozoal agent	High	Low	30; 120; 250	III*	[12,200]
<i>Norethisterone hormone</i>	<i>High</i>	<i>High</i>	1 (+0.035 Ethinylestradiol)	<i>I*</i>	[12,165]
	<i>High</i>	<i>High</i>	5	<i>I*</i>	
Praziquantel antihelmentic	Low	High	150; 600	II*	[12,16,30]
<i>Proguanil antimalarial</i>	<i>High</i>	<i>High</i>	100 (hydrochloride)	<i>I*</i>	[12,165]
<i>Pyridoxine vitamin</i>	<i>High</i>	<i>High</i>	25 (hydrochloride)	<i>I</i>	[12,16,201]
Reserpine antihypertensive	High	Low	0.1; 0.25	III	[12,16]
Rifampicin antituberculous	Low	High	150; 300	II*	[12,25,68,163,164]

^a Italics denotes class I drugs according to the FDA criteria; bold text denotes class III drugs with permeabilities corresponding to at least 80% absorption.
* First pass effect; ** Degradation in the GI-Tract; # active transport.

Table 3
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: drugs with inconclusive data

Drug	Solubility	Permeability	Dose (mg)	BCS class ^a	References
Albendazole antiparasitic	Low	Low/High	400	II/IV*	[25,202–206]
Amitriptyline antidepressive	Low/High	High	25 (hydrochloride)	I/II*	[12,16,24,207–209]
Artemether + Lumefantrine antimalarial agents	Low	Low/High	20 + 120	II/IV*	[12,30,33,210–213]
Atropine Sulphate parasympatholytic	High	Low/High	1	I/III*	[12,16,23,32,70,214]
Chlorpheniramine antihistamine	High	Low/High	4 (Hydrogenmaleat)	I/III*	[12,16,41,151,215]
Chlorpromazine antidepressive	Low	Low/High	100 (hydrochloride)	II/IV*	[12,16,24,216,217]
Ciprofloxacin antibiotic	Low	Low/High	250 (Hydrochlorid)	II/IV*	[12,17,24,218–222]
Clofazimine antibacterial agent	Low	Low/High	50; 100	II/IV	[69,223,224]
Clomiphene hormone	High	?	50 (citrate)	I/III	[12,16]
Clomipramine antidepressive	High	Low/High	10; 25 (hydrochloride)	I/III*	[12,225,226]
Dexamethasone glucocorticoide	High	Low/High	0.5; 4	I/III*	[12,16,69,227–230]
Diloxanide antiprotozoal agent	Low	Low/High	500 (furoate)	II/IV**	[12,16,231]
Efavirenz antiviral	Low	Low/High	50; 100; 200	II/IV	[31,33,232]
Ethinylestradiol hormone	High	Low/High	0.03 (+0.15 Levonorgestrel) 0.05 (+0.25 Levonorgestrel) 0.01; 0.05;	I/III*	[12,116,233]
Folic acid	Low	Low/High	1; 5	II/IV	[12,30,234,235]
Glibenclamide antidiabetic	Low	Low/High	2.5; 5	II/IV	[12,25,38,236]
Glyceryl Trinitrate Angina pectoris	High	Low/High	0.5	I/III*	[12,237,238]
Haloperidol neuroleptic	Low	Low/High	2; 5	II/IV*	[12,16,30,70,239–243]
Isosorbid dinitrate Angina pectoris	High	Low/High	5	I/III	[16,30,244,245]
Ivermectin anthelmintic	Low	Low/High	3; 6	II/IV	[12,16,30]
Lamivudin antiviral	High	Low/High	150	I/III	[7,246–248]
Levamisole anthelmintic	High	Low/High	50; 150 (Hydrochlorid)	I/III	[202,249–251]
Lopinavir antiviral	Low	Low/High	133.3 (+33.3 Ritonavir)	II/IV*	[30,252]
Mebendazole anthelmintic	Low	Low/High	100; 500	II/IV	[25,253,254]
Mefloquine antimalarial	Low	Low/High	250 (hydrochloride)	II/IV	[16,255]
Metoclopramide prokinetic agent	High	Low/High	10 (hydrochloride)	I/III*	[12,256–260]
Morphine sulfate pain relief	High	Low/High	10	I/III*	[12,16,261–264]
Niclosamide anthelmintic	Low	Low/High	500	II/IV	[12,265]
Nystatin antifungal	Low/High	Low	100 000 IU; 500 000 IU (~5000 IU = 1 mg) - > ~20–100 mg	III/IV	[12,30,33]
Pyrantel anthelmintic	Low	Low/High	250 (embonate)	II/V	[12,165]
Pyrimethamine Toxoplasmosis	Low	Low/High	25	II/IV	[12,266,267]
Quinine antimalarial	High	Low/High	300 (bisulfate or sulfate)	I/III	[12,176,268,269]
Retinol vitamin	Low	Low/High	10 000 IU (palmitate) (5.5 mg) 200 000 IU (palmitate) (110 mg)	II/IV*	[12,270,271]
Senna laxative	?	?	7.5 (sennosides)		[12]
Sodium iodide iodine deficiency	High	???	60	I/III	[12]
Spironolactone diuretic	Low	Low/High	25	II/IV*	[12,16,35,272,273]
Sulfadiazine antibacterial agent	Low	Low/High	500	II/IV	[12,23,274,275]
Sulfasalazine Colitis Ulcerosa/Morbus Crohn	Low	Low/High	500	II/IV	[12,16,276,277]
Triclabendazole anthelmintic	Low	Low/High	250	II/IV	[32,278]
Verapamil hydrochloride Ca-channel blocker	Low/High	High	40; 80 (hydrochloride)	I/II*	[1,12,16,38,70,131,221,279–282]
Warfarin Sodium anticoagulant	Low/High	High	1; 2; 5 (sodium salt)	I/II	[12,16,41,46,221,283]

^aFirst pass effect; ** Degradation in the GI-Tract; * active transport.

bioavailability greater than 90%. In cases where the bioavailability was lower than 90%, the influence of the above-mentioned factors has to be taken into account. Where low bioavailability (<90%) could be attributed with certainty to degradation in the GI-tract or because of a first-pass effect, these findings have been marked in the tables with asterisks. Data based on experiments where the amount of drug was measured by urinary excretion sometimes lacked i.v. comparison or determination of metabolites, both

of which are necessary for a sure classification of the permeability characteristics.

Good data was found in papers using the intestinal perfusion technique in humans, as these provided direct permeability data. Data from experiments with cell culture monolayers (mostly Caco-2 cells) were often available. However, absolute values reported can vary by orders of magnitude among laboratories [3] and unless the methodology is validated according to the FDA biowaiver

guidance, it is difficult to assign the drug to 'high' or 'low' permeability with certainty. Therefore, Caco-2 cell data was considered in most cases as supplementary rather than primary information.

Of the 130 orally administered drugs found in the WHO list, 61 could be classified reliably (49%). Twenty-one of these 61 (34%) were classified as class I drugs, 10 as class II drugs (17%), 24 as class III drugs (39%) and 6 as class IV drugs (10%). Taking into account drugs with provisional classification (Table 2) as well as certain (Table 1) classification, a total of 89 drugs could be classified. Thirty-two of these are class I drugs (36%), 15 class II drugs (17%), 34 class III drugs (38%) and 8 are class IV drugs (9%).

A considerable number of the orally administered drugs were classified as class I drugs, namely 32. These are highlighted in italics in the tables. These are potential candidates for consideration of a biowaiver for solid, orally administered dosage forms. Of the 34 drugs assigned to class III in Tables 1 and 2, 13 had a permeability consistent with >80% oral absorption and therefore might be additionally considered as potential candidates for biowaivers. These are highlighted in bold in the tables.

The information provided here should help pharmaceutical manufacturers of generic drug products to lower the cost of bringing a product onto the market. This is of particular interest in countries with highly restricted health care budgets. Of course, to be considered for a biowaiver other drug product characteristics, such as the therapeutic index of the drug and the potential influence of the excipients on the rate or extent of absorption, have to be considered as well.

Further research on the provisionally or indecisively classified drugs should be encouraged to increase the quality and certainty of the data. In fact, an ongoing and thorough analysis of the literature for every drug should be conducted and the findings carefully evaluated by specialists in the pertinent field. This will enable a detailed risk analysis and lead to recommendations as to whether a specific drug/drug product can be considered for a biowaiver or not. Coordination of WHO activities with those of the special interest group 'Bioavailability/Bioequivalence' of the International Pharmaceutical Federation on the field application of the BCS, as well as general issues of bioequivalence, has been initiated.

Acknowledgements

This work was partially funded by the World Health Organization and forms the basis of a Working Document on the BCS Classification of the Essential Medicines List.

The opinions expressed in this article are those of the authors and do not necessarily represent the decisions or stated policy of the World Health Organization.

Note added in proof

A review of the data and additional information revealed that, for three compounds, the certainty of the classification did not justify inclusion in Table 1. These compounds have been moved to Table 2. Further, for two additional compounds, the classification of either the permeability or solubility was reevaluated. These changes are reflected in the current tables.

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