Reviewer No. 1
Application for Addition of Atazanavir for Treatment of HIV-infection

(1) Have all important studies that you are aware of been included?

Yes X No □

If "No", add missing references with brief summary of key findings.

(2) Is there adequate evidence of efficacy for the proposed use?

Yes X* No □

* OBS: The existing studies show moderate methodological quality.

(3) Is there evidence of efficacy in diverse settings and/or populations?

Yes X No □

If "No", suggest what is needed.

(4) Are there adverse effects of concern?

Yes □ No X

If "Yes", (list / describe)

(5) Are there special requirements or training needed for safe/effective use?

Yes X No □

If "Yes", describe.
Requirements of HIV services where facilities are available to perform confirmation tests of HIV infection status, co-morbidities and opportunistic infections, measurement of virologic and immunologic efficacy and safety. Health personnel should be trained for monitoring adherence and therapy results.

(6) Is this product needed to meet the majority health needs of the population?

Yes No X

If "No", is there a special reason why this should be on the Model List?

HIV-infection is a pandemic disease, with a wide global distribution, and the availability of its adequate treatment is an issue of public health relevance.

(7) Is the proposed dosage form registered by a stringent regulatory authority?

Yes X No □

If "No", give details.
(8) What action do you propose for the Committee to take?

Taking account of comparable virologic efficacy of atazanavir boosted or unboosted with lopinavir/ritonavir and other PIs either in ARV-experienced patients or in ARV-naïve patients, acceptable safety and once daily dosing versus an unfavourable cost-effectiveness and budget impact, I recommend the members of the Committee to weigh the real advantages of atazanavir before deciding for its inclusion in the WHO Model List.

(9) Additional comment, if any.

Based in moderate quality-evidence, atazanavir combined with ritonavir is recommended as an alternate to lopinavir/ritonavir fixed dose combination (LPV/r) in second-line treatment as well as in first-line highly active antiretroviral therapy, especially for the subset of patients with greater cardiovascular risk, since atazanavir has a better lipid profile. Nevertheless, extended atazanavir use resulted in lipid changes that were not clinically relevant. Additionally, ritonavir boosting of atazanavir may result in some elevation of lipids. Improved serum lipids due to atazanavir therapy are not associated with improvement of endothelial function and there is no evidence of related less frequent coronary heart disease events (relevant clinical outcome) in patients that have taken atazanavir regimens. If once daily dosing contributes to adherence on a long-term basis, this could be a significant advantage of atazanavir, since there is evidence that incomplete adherence to modern HAART over time was strongly associated with increased mortality. On the other hand, the fixed dose combination LPN/r new adult tablet formulation – that not requires refrigerated storage, is less expensive and reduces the number of dosage units administered per day – might be able to improve patient adherence. Another issue to be considered positively: the inclusion of atazanavir/ritonavir could enhance the availability of multiple antiretroviral agents in the estimated increase of HIV-infected patients that will need second-line regimens. (See below references in a short-review).
APPLICATION FOR ADDITION OF ATAZANAVIR FOR THE TREATMENT OF HIV-1 INFECTION

Background

In 2007, the 15th Report of the WHO Expert Committee No. 946 recommended the review of a protease inhibitors section. The Committee stated that “selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience”.

The subsection 6.4.2.3 of the 15th Essential Medicines List includes four isolated protease inhibitors and one combination: indinavir (IDV), nelfinavir (NFV), ritonavir, saquinavir (SQV) and lopinavir + ritonavir (LPV/r).

First-line highly active antiretroviral therapy (HAART) includes two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI) with one non nucleoside reverse transcriptase inhibitor (NNRTI) or at least one protease inhibitor (PI). The majority of currently available protease inhibitors are coadministered with low-dose ritonavir as a pharmacoenhancer that significantly increases protease inhibitor plasma concentrations.

Second-line antiretroviral therapy is recommended in patients with virologic, immunologic or clinical failures. Special concern exists when there are previous multiple failures. The therapy after the first failure includes two NRTI, one NNRTI and one PI ritonavir-boosted. The preferred PI is ritonavir-boosted lopinavir (LPV/r) for its higher experience of use and lower comparative cost.

Unboosted atazanavir - a highly active azapeptide inhibitor of the HIV protease - is approved, as an alternative, for first-line HIV therapy in adults in the United States. The pharmacoenhancing effect of ritonavir on atazanavir resulted in a sufficient genetic barrier to viral resistance. So the combination is recommended for the second-line therapy of HIV-1 infection in HIV-1-infected adult patients in the United States and the European Union.

Application

The WHO Department of HIV/AIDS proposed to include atazanavir in the Model List, as 100 mg and 300 mg capsules, regarding its improved safety related to metabolic effects and its convenience (once daily dosing) for the patient.

Comments

EFFICACY

In treatment-experimented HIV-1-infected patients

A randomized, open-label, multinational, 48-week study compared unboosted atazanavir 400 mg once daily versus lopinavir 400 mg boosted with ritonavir 100 mg twice daily, in 290 HIV-infected patients who failed to respond to a previous regimen with one PI and two NRTIs. Lopinavir/ritonavir resulted in a significantly greater reduction in HIV RNA than unboosted atazanavir (-2.02 vs. -1.59 log10 copies/ml; P < 0.001) at week 48. However, both regimens demonstrated comparable virologic suppression in subjects who had no baseline NRTI mutations.

An open-label, randomized, multinational trial (BMS Study 045) compared once-daily atazanavir/ritonavir (300/100 mg) and twice-daily lopinavir/ritonavir (400/100 mg) in HIV-infected patients with multiple virologic failures. All of them also received one NRTI. Over 96 weeks, the ATV/RTV regimen demonstrated similar virologic efficacy to the LPV/RTV regimen.

The SWAN (Switch to Another Protease Inhibitor) study, a 48-week, open-label trial involving HIV-positive patients with virologic suppression who were receiving stable PI-based regimens (with or without ritonavir), randomised patients to switch to atazanavir-containing regimen (278 patients) or to continue their previous PI-containing regimen (141 patients). If they were
receiving tenofovir, they switched to atazanavir-ritonavir (300/100 mg per day). The proportion of patients who experienced virologic rebound was significantly lower among those who switched to an atazanavir-containing regimen (7%) than it was among those who continued to receive a comparator PI regimen (16%; \( P=0.004 \)).

An open-label, 48 weeks of follow-up trial (SLOAT) \(^5\) randomised patients receiving lopinavir/ritonavir-based regimens and having undetectable plasma HIV-RNA for longer than 24 weeks to continue on the same therapy (n=87) or switch to atazanavir (400 mg once daily [49]) or atazanavir/ritonavir (300/100 mg once daily due to concomitant tenofovir use [53]). All patients received the PI along with two nucleoside analogues. The replacement of lopinavir/ritonavir by atazanavir provides similar virological failure (9 and 12 patients, respectively).

**In naïve-treatment HIV-1-infected patients**

The CASTLE study\(^6\) compared once-daily atazanavir/ritonavir (300/100 mg) versus twice-daily lopinavir/ritonavir (400/100 mg), each in combination with fixed-dose tenofovir/emtricitabine (300/200 mg once daily), for management of antiretroviral-naïve HIV-1-infected patients (n=883) through 48 week. At week 48, atazanavir/ritonavir once-daily demonstrated similar antiviral efficacy to lopinavir/ritonavir twice-daily (78% versus 76% patients, respectively, had achieved a viral load of less than 50 copies per mL). The same similarity was evidenced in the mean increase in CD4 cell count and in number of patients with virological failures.

Another randomised, open-label, 96-week trial\(^7\) compared unboosted atazanavir (400 mg, once daily) to atazanavir plus ritonavir (300 mg and 100 mg, once daily) in ARV-naïve HIV-infected patients. Both regimens included lamivudine and an investigational extended-release formulation of stavudine. The primary endpoint for this noninferiority study was the proportion of patients (response rate) with an HIV RNA load <400 copies/mL at week 48. Response rates at week 48 were 86% and 85% on the ATV300/RTV and ATV400 regimes, respectively (difference estimate = 1.5; 95%CI: -8.2 - 11.1). There were 3 and 10 patients with virologic failure in the ATV300/RTV and ATV400 groups, respectively.

An observational cohort analysis (n=443)\(^8\) of atazanavir use (comparing ritonavir-boosted to non-boosted) in antiretroviral-naïve patients initiating atazanavir were followed through 52 weeks of treatment. Ritonavir-boosted atazanavir was associated with greater virologic control and immune response through 52 weeks compared to non-boosted atazanavir. Thus, the authors favoured ritonavir-boosted atazanavir prescribing.

**SAFETY**

Atazanavir is expected to overcome the problems of earlier protease inhibitors, such as unfavourable adverse events like hyperlipidemia, diarrhea and lipodystrophy\(^1\). This better metabolic profile could be particularly attractive for the subset of patients with greater cardiovascular risk.

However, specific side effects were identified during clinical practice, such as an increased rate of patients with jaundice, and, more recently, genetic risk factors causing hyperbilirubinaemia with or without jaundice, but seldom results in the need to discontinue treatment. Atazanavir inhibits glucuronyltransferase, an enzyme responsible for the metabolism of bilirubin in liver, thus increasing unconjugated bilirubin levels in blood\(^1\).

Another disadvantage of atazanavir is its interaction with acid-reducing agents, in particular proton-pump inhibitors.

**In treatment-experimented HIV-1-infected patients**

In BMS-043 study\(^2\) the unboosted atazanavir 400 mg once daily, from baseline to week 48, resulted in either no change or decreases in fasting LDL cholesterol, total cholesterol, and fasting triglycerides, whereas lopinavir/ritonavir resulted in increases (\( P < 0.05 \), all between-treatment comparisons). Atazanavir-treated patients required less frequent lipid-lowering therapy (6% vs. 20% for lopinavir/ritonavir).

In BMS Study 045\(^3\) - designed to evaluate the efficacy and safety of ATV/RTV versus LPV/RTV in treatment-experienced patients – a follow-up over 96 weeks demonstrated that the LPV/RTV regimen significantly increases total cholesterol (+9%) and fasting triglycerides (+30%) in comparison with the ATV/RTV regimen, which decreases these parameters (-7% and -2%, respectively).
respectively; $P < 0.0001$). Diarrhoea occurred less frequently in ATV/RTV patients (3%) in comparison with LPV/RTV patients (13%) ($P < 0.01$). Elevations in bilirubin were more common in ATV/RTV patients (53%) than LPV/RTV patients (<1%) with no resulting discontinuations.

In the SWAN study$^4$ patients who switched to atazanavir therapy experienced significantly less total cholesterol, fasting triglyceride, and non-high density lipoprotein cholesterol elevations than did patients in the comparator PI group ($P<0.001$). Related to patients who continued their prior PI-based regimen, those receiving atazanavir had comparable rates of adverse event-related discontinuation and serious adverse events through 48 weeks.

In SLOAT study,$^5$ the replacement of lopinavir/ritonavir by atazanavir provides an overall significant reduction ($P < 0.001$) in median total cholesterol and triglycerides after 48 weeks of atazanavir switching. Greater reductions in total cholesterol and triglycerides were seen in patients switched to atazanavir without ritonavir boosting.

A randomised, observer-blind, treatment-controlled trial$^6$ investigated 39 HIV-infected patients randomly assigned to continue the current PI or change to unboosted atazanavir. After 24 weeks of treatment, the switch from another PI to atazanavir in treatment-experienced patients did not result in improvement of endothelial function despite significantly improved serum lipids. Total cholesterol improved in both groups, but changes were more pronounced on atazanavir ($P = 0.05$, changes between groups). High-density lipoprotein and triglyceride levels improved on atazanavir ($P = 0.03$ and $P = 0.003$, respectively) but not in controls.

In naïve-HIV-1-infected patients

In the CASTLE study,$^6$ serious adverse events were noted in 51 (12%) of 441 patients in the atazanavir/ritonavir group and in 42 (10%) of 437 patients in the lopinavir/ritonavir group. Fewer patients in the atazanavir/ritonavir group than in the lopinavir/ritonavir group experienced diarrhoea (2% vs. 11%) and nausea (4% vs. 8%). However jaundice and hyperbilirubinemia were mainly seen in patients in the atazanavir/ritonavir group.

In the 089 study,$^7$ adverse event-related discontinuations were 8% among ATV300/RTV-treated patients and <1% among ATV400-treated patients. Plasma lipid elevations were low with both regimens. Both regimens were well tolerated.

Another 48-week, randomized trial,$^8$ performed in antiretroviral-naïve patients, compared atazanavir (n=111) and efavirenz (n=100) concerning body fat and other metabolic side effects. Each agent was administered with fixed-dose zidovudine (300 mg) and lamivudine (150 mg) given twice daily. Both treatments resulted in minimal to modest increases in fat accumulation, as demonstrated in several measurements. Atazanavir was not associated with none metabolic disturbances commonly related to lypodistrophy.

A report$^9$ presented the results of two randomized, blinded, 48-week trials that compared the frequency and severity of dyslipidemia of atazanavir and nelfinavir in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in antiretroviral (ARV)-naïve patients. Lipid levels remained within baseline ranges at week 48 with atazanavir treatment, whereas clinically relevant elevations in total cholesterol, fasting LDL-cholesterol, and fasting triglyceride concentrations occurred with nelfinavir treatment. After 48 weeks, there was a substantive increase in the proportion of nelfinavir-treated patients who would be recommended for lipid-lowering treatment, differently from atazanavir-treated patients.

**CONVENIENCE**

Atazanavir was the first once-daily applied protease inhibitor approved for the treatment of HIV-1 infection. Atazanavir is available in United States, European Union, Latin America, India and six African countries.

For therapy of ARV-naïve HIV-infected patients atazanavir alone can be taken at 400 mg once daily, with food. Atazanavir 400 mg day is rapidly absorbed when taken with a light meal. In these patients, atazanavir boosted with ritonavir (ATV/r 300/100 mg) is recommended if combined with either tenofovir, efavirenz, an H2-receptor antagonist or a proton pump inhibitor.

For therapy-experienced patients the recommended dose is ATV 300 mg with ritonavir 100 mg, taken once daily with food. In PI treatment-experienced patients with PI mutations, susceptibility
to ATV is usually reduced, so it should be administered with ritonavir. Coadministered with ritonavir on a once-daily dosage regimen, minimum plasma concentration was increased in comparison with atazanavir alone. Therefore, ritonavir-boosted atazanavir regimen is increasingly favoured in some patients, for instance in those receiving efavirenz that decreased atazanavir concentrations by 75% or tenofovir that decreased atazanavir concentrations by 25%. Also H2-receptor antagonists and proton pump inhibitors lead to significantly lower plasma levels of atazanavir. If combined with tenofovir and an H2-receptor antagonist, the recommended dose is ATV 400 mg with ritonavir 100 mg. It is recommended that proton pump inhibitors should not be used in treatment-experienced patients receiving atazanavir.

Major advantages of atazanavir to date are its simplicity of administration (once-daily dosing) and its less undesirable effect on the lipid profile. No elevations in serum levels of total cholesterol, low-density lipoprotein cholesterol or triglycerides have been observed with unboosted ATV. Although some increases in these levels are found with boosted ATV, these were lower when compared with other PIs.

If once daily dosing contributes to adherence on a long-term basis, this could be a significant advantage, since there is evidence that incomplete adherence to modern HAART over time was strongly associated with increased mortality.

COST

In pre-treated HIV-1-infected patients

A cost effectiveness study evaluated long-term combined effects of HIV disease and antiretroviral (ARV) therapy-related risk for coronary heart disease (CHD) on quality-adjusted survival and healthcare costs in the US for ARV-experienced patients receiving lopinavir/ritonavir (LPV/r) or ritonavir-boosted atazanavir (ATV+RTV) as the protease inhibitor (PI) in their ARV regimens. Using LPV/r capsules was comparatively beneficial for ARV-experienced patients in quality-adjusted life-months (QALMs) of 4.6 (corrected for differences in CHD risk) compared with ATV+RTV. In addition, there were 5- and 10-year overall per-patient cost savings of $US 17,995 and $US 21,298, respectively. Estimates for the LPV/r tablet formulation approved in 2005 (assuming similar efficacy) improved cost savings over 5- and 10-year periods to $US 19,598 and $US 23,126 per patient, respectively, because of a drug price differential. Sensitivity analysis tested numerous assumptions about the model cost and efficacy parameters and found that the results were robust to most changes. The study concluded that LPV/r appears to be a highly cost-effective regimen relative to ATV+RTV for the treatment of HIV. The long-term CHD risk associated with LPV/r was minimal.

The same authors performed a same model analysis in UK, Spain, Italy and France, evaluating cost effectiveness and expected budget impact of lopinavir/ritonavir compared with atazanavir plus ritonavir in antiretroviral-experienced patients. Also, this study set out to estimate the long-term combined effects of HIV disease and antiretroviral-related risk for CHD on quality-adjusted survival and healthcare costs for antiretroviral-experienced patients. LPV/r was a highly cost-effective regimen relative to ATV+RTV for the treatment of HIV for each of the four countries examined in the study. The effect of LPV/r on long-term CHD risk was minimal. The cost of lipid-lowering drugs and treatment for CHD was insignificant compared with the overall cost savings from LPV/r therapy.

In naïve-HIV-1- infected patients

A cost-effectiveness analysis and budget impact analysis comparing lopinavir plus ritonavir (LPV/r) and atazanavir plus ritonavir (ATV+RTV) for antiretroviral-naïve patients as reported in the CASTLE study concluded that the use of an LPV/r-based regimen appears to be more cost-effective compared with an ATV+RTV-based regimen. The coronary heart disease events risk differences (based on percent of patients with total cholesterol >240 mg/dL) in favour of ATV+RTV resulted in an average improvement in life expectancy of 0.031 quality-adjusted life years (QALYs) (11 days), and an incremental cost-effectiveness ratio of $1,409,734/ QALY. Use of the LPV/r regimen saved $24,518 and $36,651 at 5 and 10 years, respectively, with lifetime cost savings estimated at $38,490. A sensitivity analysis estimated an average improvement in life expectancy of 31 quality-adjusted days in favour of ATV+RTV, and a cost-effectiveness ratio of $520,861/QALY. So, the very small added coronary heart disease events risk predicted by LPV/r treatment is more than offset by the
substantial short- and long-term cost savings expected with the use of LPV/r in antiretroviral-naïve individuals with average to moderately elevated CHD risk.

Since the previous pharmaco-economic studies were performed in developed countries, the results may not necessarily be applicable to resource-poor countries.

Cost is an important issue that influences HIV-treatment support in middle and low-income countries, especially in those that have scaled up wide and unrestricted distribution. In a recent document of Ministry of Health in Brazil, the mentioned prices per day of lopinavir/ritonavir and atazanavir/ritonavir are US$ 2,740 and US$ 6,102, respectively.

Conclusions

Unboosted atazanavir

- Unboosted atazanavir (or ritonavir-boosted atazanavir for patients receiving tenofovir) significantly reduced virologic rebound in patients with virological suppression obtained with PI-based regimens but who switched to atazanavir-containing regimen. Similar designed study found that the replacement of lopinavir/ritonavir by atazanavir provides similar virological failure and a significant reduction in serum lipids.

- In treatment-naïve HIV-1-infected patients, unboosted atazanavir is as effective and tolerable as atazanavir/ritonavir, as part of once-daily highly active antiretroviral therapy regimens. On the other hand, a cohort found greater virologic control and immune response associated with atazanavir/ritonavir versus unboosted atazanavir.

- Unboosted atazanavir demonstrated no changes or greater reductions in total cholesterol and triglycerides in comparison to boosted atazanavir and other PI-regimens in treatment-experienced HIV patients and in treatment-naïve HIV patients.

Atazanavir plus ritonavir

- In treatment-naïve HIV-1-infected patients as well as in treatment-experienced HIV-1-infected patients, atazanavir plus ritonavir once-daily demonstrated similar antiviral efficacy to lopinavir/ritonavir twice-daily.

- Atazanavir plus ritonavir is preferred to unboosted atazanavir in PI treatment-experienced patients with PI mutations and in those receiving efavirenz, tenofovir, H2-antagonists or proton pump inhibitors which lead to significantly lower plasma levels of atazanavir.

- Atazanavir/ritonavir once-daily demonstrated lesser gastrointestinal toxicity (diarrhea and nausea) and more favourable lipid profile, but higher rate of hyperbilirubinaemia and jaundice (with no resulting discontinuations) than lopinavir/ritonavir twice-daily in treatment-experienced patients. Despite significantly improved serum lipids there was no improvement of endothelial function.

- Atazanavir/ritonavir is comparatively as beneficial as lopinavir/ritonavir for ARV-experienced patients in quality-adjusted life-months, but highly less cost effective, either in ARV-experienced patients or in ARV-naïve patients.
Recommendation

Based in moderate quality-evidence, atazanavir combined with ritonavir is recommended as an alternate to lopinavir combined with ritonavir (LPV/r) in second-line treatment as well as in first-line highly active antiretroviral therapy, especially for the subset of patients with greater cardiovascular risk due to its better lipid profile. Nevertheless, improved serum lipids showed in atazanavir therapy are not associated with improvement of endothelial function and there is no evidence of related less frequent coronary heart disease events (relevant clinical outcome). Its convenience is an advantage to be considered. If once daily dosing contributes to adherence on a long-term basis, this could be a significant advantage, since there is evidence that incomplete adherence to modern HAART over time was strongly associated with increased mortality. Another issue to consider positively is the availability of multiple antiretroviral agents in the estimated increase of HIV-infected patients that will need second-line regimens.

Taking account of comparable virologic efficacy of atazanavir boosted or unboosted with lopinavir/ritonavir and other PIs either in ARV-experienced patients or in ARV-naïve patients, acceptable safety and once daily dosing versus an unfavourable cost-effectiveness and budget impact, I recommend the members of the Committee to balance the real advantages before deciding for the inclusion of atazanavir in the WHO Model List.

References


