Reviewer No. 1 checklist for review of: Protease inhibitors in the WHO Essential Medicines List

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

Yes ☐ No ✓

This is not a standard data-driven application, but will be dealt with taking into cognisance other WHO materials and accessible evidence. A variety of proposals are included:

A. To remove all formulations of nelfinavir (NFV) from the EML
B. To add the heat-stable fixed-dose combination (FDC) formulations of lopinavir/ritonavir (LPV/r 200+50mg and 100+25mg tablets) to the EML, while retaining the existing listing of formulations that require refrigeration (133.33+33.33mg capsules and 400mg+100mg/5ml oral solution) until these have been replaced in most markets
C. To remove the 200mg and 333mg tablet formulations of indinavir (IDV) from the EML
D. To remove the 200mg hard gel capsule formulation of saquinavir (SQV) from the EML, and to replace this with the 500mg tablet formulation, but noting that this is to be used particularly for the treatment of tuberculosis co-infected HIV patients where concomitant use of a protease inhibitor with rifampicin is unavoidable.
E. To consider a separate application for the inclusion of atazanavir (ATV)
F. To add the heat-stable formulations of ritonavir (RTV 100mg and 25mg tablets) to the EML, while retaining the existing listing of formulations that require refrigeration (100mg capsule and 400mg/5ml syrup) until these have been replaced in most markets
G. To remove the 40mg tablet formulation of stavudine (d4T) from the EML
H. To add the FDC formulation of zidovudine/lamivudine/abacavir (ZDV/3TC/ABC 300mg+150mg+300mg) to the EML

It is noted that request G deals with the listing of a nucleoside reverse-transcriptase inhibitor (NRTI) and not a protease inhibitor (PI). Request E will not be dealt with in relation to this review, but as a separate application.

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

Yes ☐ No ☐

A. Irrelevant to the application, as the issue is availability and place in therapy, not efficacy per se
B. Irrelevant to the application, as the issue is availability and suitability of use, not efficacy per se
C. Irrelevant to the application, as the issue is in the place in therapy, not efficacy per se
D. Irrelevant to the application, as the issue is safety and place in therapy, not efficacy per se
E. To be considered separately
F. Irrelevant to the application, as the issue is availability and suitability of use, not efficacy per se
G. Irrelevant to the application, as the issue is safety, not efficacy per se
H. The application makes mention of the evidence that the “triple nuke” combinations are less effective than combinations which include either a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or a PI. There is some evidence to back this statement.12 In November 2008, the US DHHS issued revised “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents” (see http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf) stated that “This combination is generally not recommended (BI) and should be used only when a preferred or an alternative NNRTI-based or a PI-based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.”
(3) **Is there evidence of efficacy in diverse settings and/or populations?**

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<td>The available evidence has come from a small number of comparative trials that have shown, as stated in the US DHHS guidelines &quot;comparable antiretroviral activity to indinavir-based and nelfinavir-based but was inferior virologically to an efavirenz-based regimen&quot;. However, the combination, if not the fixed-dose combination, has been widely applied in different settings.</td>
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(4) **Are there adverse effects of concern?**

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<td>The safety of boosted-saquinavir combinations in tuberculosis co-infected patients taking concomitant rifampicin has been questioned. The advice from the US DHHS guidelines is suitably cautious: “In the case of an antiretroviral therapy–experienced patient in whom NNRTI-based regimens are not an option and for whom rifabutin is not available, consultation with an HIV expert is recommended.” In May 2007, a WHO Working Group published a report entitled “Prioritizing Second-Line Antiretroviral Drugs for Adults and Adolescents: a Public Health Approach” – see <a href="http://www.who.int/entity/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf">http://www.who.int/entity/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf</a>. The advice given was as follows: “The HIV pandemic has led to a resurgence of tuberculosis and the challenge challenges of TB-HIV co-therapy for patients on second-line ART is well recognized. Management of co-infected patients has shown that TB can be cured with standard antituberculosis regimens, including the use of rifampicin-based TB treatment for 6 months,” [WHO, TB HIV: A Clinical Manual; second edition, D.o.H.A. Stop TB Department, Department of Child and Adolescent Health and Development and World Health Organization, Editor. 2004.] Preliminary evidence and experience has confirmed recommendations in WHO guidelines that for most patients, especially those with CD4 counts &lt; 100 cells/mm3, HIV treatment should not be delayed, but should be started or continued alongside TB treatment. It is expected that many patients will fail first-line ART with active TB ; and TB will develop in patients on second-line therapy. However, because of well recognized drug-drug interactions, it is difficult to use rifampicin with any boosted PI-based regimens,.[ DHHS, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2006.] For patients who need antituberculosis treatment and who are already on a boosted PI, or who need to be switched to a boosted PI based regimen, two main options exist: • Increase the ritonavir dose with some bPIs (SQV/r+RTV and LPV/r+RTV) and maintain rifampicin in the anti-TB regimen; • Substitute rifabutin for rifampicin in the anti-TB regimen and maintain the standard PI-based ART regimen. Neither option is easily implementable at present in LMIC. Currently rifabutin is considered unaffordable for most TB programs (almost US$ 2 per day). In many LMIC, rifabutin is not registered, compromising procurement at any price. Similarly, heat-stable ritonavir as a standalone medication is single sourced, and is not currently available at an affordable price.Furthermore, dose adjustments for ritonavir are difficult outside of specialized and training centres. WHO strongly supports key efforts that will enable successful treatment of HIV-TB co-infection: • Application for rifabutin to the Model List of WHO Essential Medicines should be considered; • Efforts to secure production of rifabutin at affordable prices should also be encouraged. Rifabutin is only available from a single-source, and it may have patents pending in countries with capacity of production, which could block competition and price reduction. Countries should consider use of the flexibilities included in the TRIPS agreement in order to increase access to these recommended products.”</td>
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E. To be considered separately

F. Irrelevant to the application, as the issue is availability and suitability of use, not safety per se

G. The evidence for the suggested removal of the 40mg adult dose of d4T was provided in an addendum to the 2006 WHO Guidelines on Antiretroviral Therapy for HIV Infection in Adults and Adolescents – see http://www.who.int/hiv/art/ARTadultsaddendum.pdf. Data were reviewed from 3 sources: Hill A, Ruxrungtham K, Hanvanich M et al. Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. Expert Opin Pharmacother. 2007;8(5):679-88 ; Sánchez-Conde M, Mendoza C, Jimenez-Nacher I et al. Reductions in stavudine dose ameliorate mitochondrial-associated complications without compromising antiviral activity. HIV Clin Trials 2005; 6(4):1075-90 and Wolf E, Koegl C, Hoffmann C et al. Low dose stavudine: as effective as standard dose but with less side effects. XV International AIDS Conference, Bangkok, 11-16 July 2004 [Abstract WePe BS681]. The evidence and recommendation was summarised as follows: “A systematic review of nine randomized trials and six observational cohort studies strongly suggests that stavudine-containing regimens maintain clinical and virologic efficacy when stavudine is dosed at 30 mg twice daily, and that this reduced dose is associated with lower rates of toxicity, especially peripheral neuropathy, compared to the 40 mg twice daily dose. Complementary studies have also demonstrated a significant reduction of mitochondrial DNA depletion in patients on the 30 mg twice daily dose. However, there are limited data available about reducing the incidence of lactic acidosis with this strategy. Based on available evidence, the GDG has concluded that the 30 mg formulation of stavudine, dosed twice daily, should be used for all adult and adolescent patients, irrespective of body weight. This recommendation, which was previously considered an option, is now established as the preferred approach when d4T is used as part of an ARV therapeutic regimen.”

H. The major safety concern with abacavir is hypersensitivity and this has already been considered in listing the agent separately.

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

Yes ☐ No ✔

No additional requirements are noted.

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

A. No
B. Yes
C. No
D. Yes
E. To be considered separately
F. Yes
G. No

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

Yes ✔ No ☐

(8) What action do you propose for the Committee to take?

A. That all formulations of nelfinavir (NFV) be removed from the EML on the basis of non-availability and reduced need for this agent as part of a comprehensive antiretroviral treatment (ART) programme.

B. That the heat-stable fixed-dose combination formulations of lopinavir/ritonavir (LPV/r 200+50mg and 100+25mg tablets) be added to the EML, while retaining the existing listing of formulations that require refrigeration (133.33+33.33mg capsules and 400mg+100mg/5ml oral solution) until these have been replaced in most markets.

C. That the 200mg and 333mg tablet formulations of indinavir (IDV) be removed from the EML on the basis that these formulations are not needed as part of a comprehensive antiretroviral treatment (ART) programme.

D. That the 200mg hard gel capsule formulation of saquinavir (SQV) be removed from the EML and replaced with the 500mg tablet formulation, as this agent is required (though not the most
desirable option) for the treatment of tuberculosis co-infected HIV patients where concomitant use of a protease inhibitor with rifampicin is unavoidable.

E. That the application for the inclusion of atazanavir (ATV) be considered separately.

F. That the heat-stable formulations of ritonavir (RTV 100mg and 25mg tablets) to the EML, while retaining the existing listing of formulations that require refrigeration (100mg capsule and 400mg/5ml syrup) until these have been replaced in most markets.

G. That the 40mg tablet formulation of stavudine (d4T) be removed from the EML, on the basis of its safety profile and to ensure consistency with WHO guidelines.

H. That the fixed-dose combination formulation of zidovudine/lamivudine/abacavir (ZDV/3TC/ABC 300mg+150mg+300mg) not be added to the EML, as the circumstances in which the use of this combination are needed are not common, and this need can be met with the combination of three separate products or the addition of ABC to the FDC of ZDV/3TC.

(9) Additional comment, if any.

The recommendation in relation to request H needs to be carefully considered in the light of the comment that appears in the 15th EML: “The Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms with assured pharmaceutical quality.” This recommendation would seem to run counter to the prevailing approach. However, the risks of signaling acceptance of every ARV and every FDC as “essential” need to be debated. In the same way that the availability of various strengths of ARVs and the listing of some of the older and now less-well used and necessary PIs has been considered here, so the need for this particular FDC needs to be carefully weighed.

ABC is important as a component of second-line ART options, where a thymidine analogue has been used in the first-line regimen. Examples include ABC+ddl, TDF+ABC and ABC+3TC. The May 2007 WHO Working Group report (“Prioritizing Second-Line Antiretroviral Drugs for Adults and Adolescents: a Public Health Approach” – see http://www.who.int/entity/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf) rated these as more important than AZT+3TC+ABC where a thymidine analogue was used in the first-line regimen. It noted that ZDV/3TC/ABC was potentially of greater importance where a non-thymidine analogue was used in the first-line regimen. As the particular triple combination of ZDV/3TC/ABC is only needed in a few circumstances and is known to show inferior virological potency, it should perhaps not be included on the EML as an essential FDC.

References


