WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

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1. **Summary statement of the proposal for inclusion, change or deletion:**

   This document proposes the inclusion of the tablet formulation of Atazanavir/Ritonavir 300mg/100mg (ATV/r) for treatment of HIV-1 infection among adults living with HIV/AIDS in both the WHO Essential Medicines List and the WHO Essential Medicines List for Adults.

   The principal reasons for requesting this inclusion are as follows:

   - Modern anti-retroviral therapy (ART) mandates the use of three or more drugs and this can require a large number of tablets to be swallowed each day and used lifelong.
   - According to the WHO 2010 Treatment Guidelines for HIV Infection in Adults and Adolescents, ATV/r is one of the two preferred Protease Inhibitors (PIs) for use in second-line regimens.
   - As a fixed-dose combination with once-daily dosing, this formulation versus single drug formulations, may:
     - Increase patient adherence to treatment;
     - Delay the development of resistance;
     - Lower the total cost, including production, storage, transport, dispensing and other health system costs;
     - Reduce the risk of medication errors by prescribers, dispensers or patients themselves; and
     - Simplify and increase security of supply systems

2. **Name of the focal point in WHO submitting or supporting the application:**

   Marco Vitoria, WHO/HTM/HIV/ATC

3. **Name of the organization(s) consulted and/or supporting the application:**

   Clinton Health Access Initiative, Inc.

4. **International Nonproprietary Name (INN, generic name) of the medicine:**

   Atazanavir/Ritonavir

5. **Dosage form or strength proposed for inclusion:**

   Each tablet contains atazanavir 300mg and ritonavir 100mg (WHO supported).

6. **International availability - sources, if possible manufacturers:**

   Atazanavir/Ritonavir 300mg/100mg tablets are manufactured at:

   Mylan Laboratories Limited
   F-4, F-12, Malegaon M.I.D.C
   Sinnar, Nashik 422113
   Maharashtra
   India

7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group:**

   Since Atazanavir and Ritonavir are protease inhibitors used in conjunction with an NRTI backbone, inclusion within ‘Protease Inhibitors’ (6.4.2.3) is requested.
8. Information supporting the public health relevance

8.1. Epidemiological information on disease burden:
UNAIDS reported in 2010 that 97% of the world's 33.3 million people living with HIV/AIDS (PLHIV) were in low- and middle-income countries. In 2010 there were 2.7 million new HIV-1 infections and 1.8 million AIDS-related deaths. The 2011 WHO Progress Report for HIV/AIDS indicated that at the end of 2010 there were approximately 6.65 million people in low and middle income countries on antiretroviral therapy (47% of those eligible for therapy) and 456,000 children on ART.

ATV/r 300mg/100mg, in combination with other antiretrovirals, is indicated for the treatment of HIV infection in adolescents and adults weighing over 15kg or age 6 years or older.

Assessment of current use:

Atazanavir combined with ritonavir (ATV/r) is currently used as an alternate to lopinavir combined with ritonavir (LPV/r) which is currently the dominant PI used in low and middle income countries. Currently 2.9% of patients in LMIC (excluding the Americas) are on a second line regimen and the majority of them are using LPV/r. (WHO, 2010- TUPR) However, given that the switching rate from first to second line regimens is expected to increase, the use of ATV/r is expected to increase with its wider availability in low and middle income countries after the introduction of a heat-stable generic fixed-dose combination tablet.

Target population:

HIV-1 infected adults and adolescents at least 40kg who require a protease inhibitor-containing first or second line.

9. Treatment details

9.1. Reference to existing WHO and other clinical guidelines:
ATV/r is recommended as a preferred PI for use in adult second-line regimens, in combination with an appropriate NRTI backbone.

9.2. Dosage regimen:

Adolescents and Adults 40kg and above
The recommended oral dose of ATV/r 300mg/100mg tablets for adolescents and adults is one tablet daily, in combination with other antiretroviral agents.

ATV/r 300mg/100mg tablets should be taken with food.

Dose Adjustment:
Because it is a fixed-dose tablet, ATV/r 300mg/100mg tablets should not be prescribed for patients requiring dosage adjustment unless the separate components necessary for appropriate dose adjustment are also available.

The dose of ATV/r remains the same for adults if combined with an H2-receptor antagonist. If combined with tenofovir and an H2-receptor antagonist, the recommended dose is ATV 400mg with ritonavir 100mg. It is recommended that proton pump inhibitors should not be used in treatment-experienced patients receiving atazanavir.
9.3. **Need for special diagnostic or treatment facilities and skills:**
Not needed.

10. **Summary of comparative effectiveness in a variety of clinical settings:**
In compiling the evidence it is recognized that ATV has been individually included in the WHO EML since 2009 and at that time evidence had been satisfactorily summarized and submitted for review. Likewise, ritonavir has been included as a protease-inhibitor booster in the EML since 2002 and in 2008 the 17th edition of the EML was updated to include the heat stable formulation of Ritonavir.

10.1. **Fixed-dose combination**
Antiretroviral therapy generally requires the use of three or more drugs. This often requires taking a large number of tablets/capsules each day. Fixed-dose combinations (FDCs) of ARV drugs may:

- Allow for once- or twice-daily dosing using one or two pills, reducing the pill-burden;
- Increase patient adherence to treatment;
- Delay the development of resistance;
- Lower the total cost, including production, storage, transport, dispensing and other health system costs; and
- Reduce the risk of medication errors by prescribers, dispensers or patients themselves

Please reference the WHO Adaptation Guidelines and Treatment for Adults and Adolescents Guidelines.

Co-formulation of Atazanavir and Ritonavir into an FDC has similar virologic and immunologic efficacy to the products dosed separately. As expected, overall patient satisfaction and adherence with the once-daily FDC is excellent and comparable to or better than twice-daily dosing.¹

11. **Summary of comparative evidence on safety:**

11.1. **Estimate of total patient exposure to date**
Estimates of total patient exposure to date are not available. As stated in Section 8.1 , ATV/r is currently used as an alternate to LPV/r which is the currently the dominant PI in low and middle income countries.

11.2. **Description of adverse effects/reactions**
Atazanavir/ritonavir is considered to be well tolerated.

Hyperbilirubinaemia has been observed to be associated with atazanavir. The most common event observed is an indirect unconjugated elevation of bilirubin, related to inhibition of UDP-glucuronosyl transferase.

*Adverse effects/reactions*: Abdominal pain, diarrhea, nausea, jaundice, scleral icterus, myalgia, lipodystrophy, rash, headache, asthenia, malaise, anorexia, dyspepsia, paresthesia, dizziness, taste perversion.

*Laboratory abnormalities (Grade 3 or 4)*: Total bilirubin elevation, unconjugated bilirubin elevation, neutropenia, thrombocytopenia, ALT/AST elevation.

¹ Reference.
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Warnings: Atazanavir is primarily hepatically metabolized and increased plasma concentrations were observed in patients with hepatic impairment. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. The safety and efficacy of Atazanavir has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Dose related asymptomatic prolongations in PR interval with Atazanavir have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), Atazanavir should be used with caution and only if the benefits exceed the risk. Particular caution should be used when prescribing Atazanavir in association with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances).

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients 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 if treatment had been discontinued. A causal relationship has been suggested, although the mechanism of action has not been elucidated. Haemophiliac patients should therefore be made aware of the possibility of increased bleeding.

In clinical studies, Atazanavir (with or without ritonavir) has been shown to induce dyslipidaemia to a lesser extent than comparators. The clinical impact of such findings has not been demonstrated in the absence of specific studies on cardiovascular risk. The selection of antiretroviral therapy must be guided principally by antiviral efficacy. Consultation with standard guidelines for management of dyslipidaemia is recommended.

New onset diabetes mellitus, hyperglycaemia, and exacerbation of existing diabetes mellitus have been reported in patients receiving protease inhibitors. In some of these, the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with medicinal products that have been associated with development of diabetes or hyperglycaemia.

Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving Atazanavir. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving Atazanavir should be evaluated for alternative etiologies. Alternative antiretroviral therapy to Atazanavir may be considered if jaundice or scleral icterus is unacceptable to a patient.

Nephrolithiasis has been reported in patients receiving Atazanavir. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be considered.

The relatively high frequency of diarrhoea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medications. Serious persistent vomiting and/or diarrhoea associated with ritonavir use might also compromise renal function. It is advisable to monitor renal function in patients with renal function impairment.

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
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Ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

Ritonavir should not be given to patients with decompensated liver disease. For patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal disease: Since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment.

Ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving ritonavir.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Combination antiretroviral therapy (CART), including Atazanavir (with or without ritonavir)-based CART, is associated with dyslipidaemia. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Contraindications: Atazanavir / Ritonavir 300 mg / 100 mg tablets are contraindicated in patients with known hypersensitivity to atazanavir, ritonavir, or any of the excipients.

11.3. Drug Interactions:

Atazanavir: Atazanavir is metabolised principally by CYP3A4. Co-administration of Atazanavir with ritonavir and medicinal products that induce CYP3A4 is not recommended

Co-administration of Atazanavir with simvastatin or lovastatin is not recommended.

If the co-administration of Atazanavir with an NNRTI is required, an increase in the dose of both Atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring. The concomitant use of Atazanavir and oral contraceptives should be avoided. Co-administration of voriconazole and Atazanavir with ritonavir is not recommended unless an assessment of the benefit/risk justifies the use of voriconazole. Concomitant use of Atazanavir/ritonavir and fluticasone or other glucocorticoids that are metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing’s syndrome and adrenal suppression. Co-administration of Atazanavir with proton pump inhibitors is not recommended as the absorption of atazanavir may be reduced in situations where gastric pH is increased irrespective of cause. If the combination of Atazanavir with a
proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of Atazanavir to 400 mg with 100 mg of ritonavir; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded.

**Ritonavir:** Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Co-administration of Ritonavir Tablets and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. For select medicinal products (e.g. alprazolam) the inhibitory effects of ritonavir on CYP3A4 may decrease over time. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter. The inhibitory effect of ritonavir (with or without other protease inhibitors) on P-gp activity may decrease over time (eg digoxin and fexofenadine). Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

### 11.4. Special Populations

#### Pregnancy and Lactation

**Atazanavir:** There is little data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility. Atazanavir should be used during pregnancy only if the potential benefit justifies the potential risk. It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk in the prepartum period, additional monitoring and alternative therapy to Atazanavir should be considered.

**Ritonavir:** Use of Ritonavir tablets may be considered in pregnancy only when the benefits outweigh the risk to the foetus. Ritonavir adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during treatment. It is not known if Ritonavir is excreted in human milk. Milk excretion has not been measured in the animal studies, however a study in rats showed some effects on offspring development during lactation which are compatible with excretion of ritonavir in milk in that species.

#### Geriatrics

No data is available on which to make a dose recommendation for patients over the age of 65 years.

**Atazanavir:** No dosage adjustment is needed.

**Ritonavir:** As ritonavir is primarily metabolised by the liver, ritonavir may be appropriate for use with caution as a pharmacokinetic enhancer in patients with renal insufficiency depending on the specific protease inhibitor with which it is co-administered.

#### Hepatic impairment:

Atazanavir with ritonavir has not been studied in patients with hepatic impairment. Atazanavir with ritonavir should be used with caution in patients with mild hepatic impairment. Atazanavir should not be used in patients with moderate to severe hepatic impairment. Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease. In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised when ritonavir is used as a pharmacokinetic enhancer as increased levels of the co-administered PI may occur.
12. **Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:**

**12.1. Range of costs of the proposed medicine**

As illustrated in the following table, various sources indicate an average price per patient per year (PPPY) for the ATV/r (300/100mg) tablet of USD $281.05.

<table>
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<tr>
<th>Source</th>
<th>Median/Avg Unit Price*</th>
<th>PPPY**</th>
<th>Median/Avg Unit Price*</th>
<th>PPPY**</th>
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</thead>
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<td>CHAI Ceiling Price 2012</td>
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<tr>
<td>Average of reported prices</td>
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</tr>
</tbody>
</table>

*Median or average used depending on data available from each source.

**Price per patient per year based on WHO 2010 dosing guidelines; 365 days per year.

***Pricing data in low- and middle-income countries from January 2010 through October 2011 (as of March 30, 2012).

**12.2. Comparative cost-effectiveness presented as range of cost per routine outcome**

As the table in section 12.1 indicates, this formulation offers a significant price advantage over the combined cost of the individual formulations, costing approximately 74% less in PPPY terms. Removing the high pricing for singles from the WHO GPRM and International Drug Price Indicator Guide, there remains an 18% reduction in costs.

In addition to the cost of the product itself, there is also potential freight savings associated with procuring fewer packs. Moreover, consolidation around a single product facilitates simpler management of country supply chains.

**13. Summary of regulatory status of the medicine**

The FDA first granted generic versions of ATV/r 300mg/100mg "tentative approval" status on 18 November, 2011 for purchase and use only as part of the President's Emergency Plan for AIDS Relief (PEPFAR) in resource-limited countries.


International Pharmacopoeia

**15. Proposed (new/adapted) text for the WHO Model Formulary**

Dosage forms: Tablet, 300mg/100mg