Information to be included with an application for inclusion, change or deletion of a medicine in the WHO Model List of Essential Medicines

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1. **Summary statement of the proposal for inclusion**

This document proposes the inclusion of raltegravir 400mg tablet, 100mg scored chewable tablet and 25 mg chewable tablet in both the WHO Essential Medicines List (EML) and the WHO Essential Medicines List for Children (EMLc), for treatment of HIV among children and adults living with HIV/AIDS.

The principal reasons for requesting this inclusion are as follows:

- Adults living with drug resistant HIV in resource-limited settings presently have limited options for treatment of their infection.
- Raltegravir (RAL) represents the first approved drug in the new class of integrase strand transfer inhibitors (INSTIs or integrase inhibitors)
- 2016 WHO Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommend RAL plus lopinavir/ritonavir (LPV/r) as an alternative regimen for second-line antiretroviral therapy (ART) in adults
- In the 2016 WHO Consolidated Guidelines, a regimen including RAL plus 2 NRTIs is recommended as second-line treatment for pediatric patients failing a PI-based regimen.

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

Marco Vitoria, WHO/HTM/HIV/ATC

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

Clinton Health Access Initiative (CHAI)

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

Raltegravir, ATC code: J05AX08

5. **Formulations and strengths proposed for inclusion**

Raltegravir 400 mg tablet, 100mg scored chewable tablet, 25mg chewable tablet

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

Merck Sharp & Dohme Ltd manufactures 400 mg tablets, 100 mg (scored) and 25 mg chewable tablets
Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire
EN11 9BU

Hetero Lab Ltd manufactures 400 mg tablets
Hetero Drugs Ltd.
7-2-A2, Hetero Corporate
Industrial Estates, Sanath Nagar
Hyderabad – 500 018, Telangana, INDIA
7. **Whether the listing is requested as an individual medicine or as a representative of a pharmacological class**

This medication is proposed for the ‘Antiretrovirals’ category (6.4.2). Since raltegravir (RAL) has a novel mechanism of action, it inhibits the integrase enzyme in HIV, we propose including it in a new category: ‘Integrase inhibitors’ (6.4.2.4)

8. **Information supporting the public health relevance**

8.1 **Epidemiological information on disease burden:**

As of 2015, UNAIDS reported there were 36.7 million people were living with HIV/AIDS globally, 2.1 million new HIV-1 infections, and 1.1 million HIV-related deaths. Over 95% of infected people live in low and middle income countries with inadequate resources to effectively combat the epidemic. While some countries have achieved declines in new HIV infections among adults of 50% or more, global data show that many others have not made measurable progress and others have experienced worrying increases in new HIV infections. Overall, approximately 17 million people were receiving antiretroviral therapy (ART) in 2015 but this still represents less than half of HIV infected people.

Early and effective ART not only significantly improves the health of those living with HIV, but also reduces transmission of the disease as shown in the recently reported START study. For this reason, the World Health Organization released new guidelines in 2015 calling for treatment for all people with HIV. Easy to administer, highly effective, safe treatment options remain desperately needed in many areas of the world to meet the UNAIDS 90-90-90 targets, which call for 90 percent of people living with HIV to know their status, 90 percent of those with known status to be on ART, and 90 percent of those on ART to be virally suppressed (i.e., on successful therapy) by the year 2020.

An increasing number of patients in the international setting will require second- and third-line regimens as they fail their current treatment. Earlier guidelines placed a high value on using simpler second-line regimens, ideally as heat-stable formulations and FDCs. In all cases, the drugs used in first-line therapy should determine the choice of NRTI backbone in second-line regimens. RAL fits into this second- and third-line treatment armamentarium by virtue of its effectiveness in this setting and the acceptability of its safety profile.

Despite an impressive reduction in mother to child transmission of HIV in recent years, 150,000 new pediatric infections occurred in 2015. There are now 1.8 million children living with HIV, the vast majority in sub-Saharan Africa. Evidence shows that in the absence of antiretroviral treatment (ART), over 50% of HIV-infected infants progress to AIDS and death by the age of 2 years, but the introduction of pediatric ART has changed HIV infection in children from a life-threatening illness to a chronic but manageable infection. Despite recognition of the advantages of early treatment, pediatric treatment coverage still only reaches 49% of children eligible for treatment and in 2015 an estimated 110,000 HIV/AIDS related deaths occurred in children <15 years of age. However, with increasing evidence about the beneficial effects of earlier ART initiation and the release of the 2016 WHO Consolidated Guidelines, new recommendations stress the need for early testing and treatment for all infants and children living with HIV. These guidelines include recommendations for not only pediatric initial (first-line) treatment but also recommendations for pediatric second-line treatment.

The global community, led by UNAIDS, now has a target to end the AIDS epidemic by 2030 (Fast Track ref) but the particular vulnerabilities of pediatric patients necessitate the even more ambitious goal...
of ending pediatric AIDS by 2020. These super fast-track targets aim to reach 1.6 million children with ART by 2018, with an increasing number of these children requiring second-line treatment.

In order to successfully scale-up treatment of pediatric HIV infection, it is critical that ARV dosage forms appropriate for use in infant and young children are accessible, particularly in resource limiting settings. Dispersible solid dosage forms including chewable tablets have proven to confer an advantage over liquid dosage forms in that they are more easily stored, ease administration, and support adherence in infants and young children.

Recent years has seen the development of a variety of dosage forms for pediatric ARVs but, compared to the demand for adult ARVs, children account for just 5% of patients on ART, thereby rendering the global pediatric market smaller and more vulnerable to supply disruption. The IATT Optimal Pediatric ARV Formulary and Limited-use list was first developed in 2011 to address this challenge and now provides guidance to streamline the selection of pediatric ARV dosage forms to those that conform to a list of criteria, including dosing flexibility, user-friendliness, optimization of supply chain management, and availability of quality assured products in resource limited settings. The IATT Optimal Formulary is also revised on a regular basis to reflect current WHO recommended regimens.

8.2 Assessment of current use

RAL has been widely used in treatment for HIV-infected adults in the U.S. and Europe, for treatment-experienced patients, and more recently for those starting ART. In low and middle income countries (LMICs), use of RAL containing regimen is still limited. According to a recent WHO survey on ARV use in LMICs, approximately 25,000 people with HIV on ART are using RAL in those settings, mostly as third-line therapy.

8.3 Target population

HIV-infected adults and children who have failed WHO-recommended first or second-line regimens.

9. Treatment details

9.1 Reference to existing WHO and other clinical guidelines:

The 2016 WHO Consolidated Guidelines recommend RAL plus LPV/r as an alternative regimen for second-line antiretroviral therapy (ART) in adults.

RAL plus 2 NRTIs is a recommended second-line regimen in children failing PI-based initial therapy. The USPHS Treatment Guidelines RAL in combination with other ARVs is recommended as first line therapy.

9.2 Dosage regimens and duration

Raltegravir must always be given in combination with other antiretrovirals.

The recommended dose in ART-experienced adults: RAL 400mg twice daily without regard to food.

The recommended doses in ART-experienced children is twice daily based on weight as shown below:
During testing of the chewable tablets, it was noted the chewable tablet demonstrated higher oral bioavailability, thus higher AUC, compared to the 400 mg tablet. Dosing in pediatric patients achieved the target exposures (C\text{trough}) in the majority of subjects, but some differences in exposures between formulations were observed. Pediatric patients above 25 kg administered the chewable tablets had lower trough concentrations compared to pediatric patients above 25 kg administered the 400 mg tablet formulation. Therefore, the 400 mg tablet is the recommended formulation in patients weighing at least 25 kg. The chewable tablet offers an alternative regimen in patients weighing at least 25 kg who are unable to swallow the tablet.

Hepatic impairment: Dosage adjustment is not needed in patients with mild to moderate hepatic impairment (Child-Pugh score A or B). Pharmacokinetics of RAL have not been studied in patients with severe hepatic impairment (Child-Pugh score C).

Renal impairment: Dosage adjustment is not needed in patients with renal impairment.

9.3 Need for special diagnostic or treatment facilities and skills

Not needed, the switch from first-line to second-line treatment can be made on the basis of either standard virologic studies (HIV RNA level or resistance testing, if available locally) or clinical criteria.

10. Review of benefits: summary of comparative effectiveness in a variety of clinical settings

RAL has been shown to be safe and effective in diverse patient populations enrolled in multiple clinical trials conducted internationally.\textsuperscript{7,8,9,10} Comparative effectiveness is described based on information gathered from literature search, review of U.S. package insert for Isentress\textsuperscript{®} (RAL, Merck)\textsuperscript{11} and review of the U.S. FDA Clinical Review of Isentress (raltegravir sodium).

As noted in the U.S. product label for Isentress, BENCHMRK 1 and BENCHMRK 2 were Phase 3 studies to evaluate the safety and antiretroviral activity of RAL 400 mg twice daily in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-1-infected subjects, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes of antiretroviral therapies.\textsuperscript{7} These were the studies that supported registration of RAL for treatment experienced patients. At Week 96, outcomes for the 699 subjects randomized and treated with the recommended dose of RAL 400 mg twice daily in the pooled BENCHMRK 1 and 2 studies included virologic suppression to $< 50$ copies/mL in 55% compared to 27% achieving that level of success in the OBT alone arms. The mean changes in CD4 count from baseline were 118 cells/mm\textsuperscript{3} in the group receiving RAL 400 mg twice daily and 47 cells/mm\textsuperscript{3} for the control group.

Two randomized controlled trials investigated the efficacy of RAL + LPV/r versus 2 NRTI + LPV/r in patients failing a standard NNRTI-containing first line regimen and demonstrated equivalency of the NRTI-sparing regimens. The SECOND-LINE study, demonstrated non-inferiority of RAL+LPV/r to a 2-3 NRTI
+ LPV/r containing regimen in HIV-1 infected adults failing a standard NNRTI + NRTI containing first line with no prior exposure to integrase inhibitors or protease inhibitors. At 96 weeks 80% of the RAL arm and 76% of the control arm achieved viral suppression <200 copies/ml. In the EARNEST study, good disease control was achieved in 60% of the control group and 64% of the RAL group. At 96 weeks 86% of patients in both the NRTI and RAL arms had viral suppression <400 copies/ml. Of note the EARNEST study had a third arm evaluating LPV/r monotherapy after a 12 week RAL induction period; this third arm was found to be inferior and was discontinued.

Studies comparing the effect of RAL to other antiretrovirals on multi-drug resistant HIV were not found. Studies comparing the effect of RAL to other antiretrovirals in antiretroviral-naïve adults are available, however this comparison is outside of WHO’s medical indication for RAL (i.e. use in second and third-line regimens).

Approval of RAL in pediatric patients was based on IMPAACT P1066, a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of RAL in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 to 18 years of age. Subjects were stratified by age, enrolling adolescents first and then successively younger children. Of the 126 enrolled, 96 children received the ultimately approved dose. Of those who received the approved dose, 93 (97%) subjects 2 to 18 years of age completed 24 weeks of treatment (3 discontinued due to non-compliance). At Week 24, 54% achieved HIV RNA <50 copies/mL; 66% achieved HIV RNA <400 copies/ml. The mean CD4 count (percent) increase from baseline to Week 24 was 119 cells/mm3 (3.8%).

11. Review of harms and toxicity: summary of the evidence on safety

11.1 Description of adverse effects/reactions

The safety and tolerability profile of RAL is favorable. The most common adverse events noted in adults receiving RAL were abdominal distension, diarrhea, nausea, vomiting, fatigue, pyrexia, and headache. Overall, the safety profile in pediatric patients is similar to that observed in adults.

Severe, potentially life-threatening, and fatal skin reactions have been reported rarely. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. RAL should be discontinued if these events occur.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with RAL. Myopathy and rhabdomyolysis have been reported. RAL should be used with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase.

11.2 Identification of variation in safety due to health systems and patient factors

No clinically significant differences in safety have been identified due to differences in health systems and patient factors.

11.3 Summary of comparative safety against comparators

During the adult registrational trials, headache was the only adverse reaction of moderate to severe intensity occurring in >2% of patients receiving RAL and more than in comparison group. The rates of discontinuation due to adverse events were 4% in subjects receiving RAL and 5% in subjects receiving
placebo/OBT. As the pediatric clinical trial was a single-arm study, pediatric comparative safety information is not available. However, the overall safety of RAL in pediatric patients was noted to be similar to that observed in adults.

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

A. As illustrated in the following table, various sources indicate an average price per patient per year (PPPY) for the RAL tablet (400mg) of USD ~$642.

<table>
<thead>
<tr>
<th>Source</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Médecins Sans Frontières Price, July 2016</td>
<td>$0.925</td>
<td>$675</td>
<td>$0.125</td>
<td>$46</td>
<td>$0.100</td>
<td>$73</td>
<td>$0.156</td>
<td>$57</td>
<td>$0.109</td>
<td>$73</td>
</tr>
<tr>
<td>Global Fund Pricing, July 2016</td>
<td>$0.833</td>
<td>$608</td>
<td>$0.142</td>
<td>$52</td>
<td>$0.107</td>
<td>$78</td>
<td>n/a</td>
<td>n/a</td>
<td>$0.131</td>
<td>$96</td>
</tr>
<tr>
<td>CHAI Reference Price, 2016</td>
<td>n/a</td>
<td>n/a</td>
<td>$0.150</td>
<td>$55</td>
<td>$0.110</td>
<td>$80</td>
<td>n/a</td>
<td>n/a</td>
<td>$0.142</td>
<td>$103</td>
</tr>
<tr>
<td>Average of reported prices</td>
<td>$0.879</td>
<td>$642</td>
<td>$0.139</td>
<td>$51</td>
<td>$0.106</td>
<td>$77</td>
<td>$0.156</td>
<td>$57</td>
<td>$0.124</td>
<td>$91</td>
</tr>
</tbody>
</table>

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

B. As illustrated in the following table, based on Médecins Sans Frontières reference price for Merck, the price per patient per year (PPPY) for the RAL chewable tablet (100mg) was USD ~$426.

<table>
<thead>
<tr>
<th>Source</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
<th>Price/Unit (USD)</th>
<th>PPPY (USD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Médecins Sans Frontières Price, July 2016</td>
<td>$0.583</td>
<td>$426</td>
<td>$0.099</td>
<td>$145</td>
</tr>
<tr>
<td>Global Fund Pricing, July 2016</td>
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<td>n/a</td>
<td>$0.083</td>
<td>$122</td>
</tr>
<tr>
<td>CHAI Reference Price, 2016</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Average of reported prices</td>
<td>$0.583</td>
<td>$426</td>
<td>$0.091</td>
<td>$133</td>
</tr>
</tbody>
</table>

*Price per patient per year WHO dosing guidelines for the 14.0 – 19.9 kg weight bands; 365 days a year

C. As illustrated in the following table, based on Médecins Sans Frontières reference price for Merck, the price per patient per year (PPPY) for the RAL chewable tablet (100mg) was USD ~$657.
WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

<table>
<thead>
<tr>
<th>Source</th>
<th>RAL Chewable Tablet (25mg)</th>
<th>LPV/r FDC Tablet (100/25mg)</th>
<th>LPV/r Oral Solution (80+20mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Médecins Sans Frontières Price, July 2016</td>
<td>$0.300 $657</td>
<td>$0.099 $108</td>
<td>$0.103 $150</td>
</tr>
<tr>
<td>Global Fund Pricing, July 2016</td>
<td>n/a</td>
<td>$0.083 $91</td>
<td>$0.103 $150</td>
</tr>
<tr>
<td>CHAI Reference Price, 2016</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a n/a</td>
</tr>
<tr>
<td>Average of reported prices</td>
<td>$0.300 $657</td>
<td>$0.091 $100</td>
<td>$0.103 $150</td>
</tr>
</tbody>
</table>

*Price per patient per year WHO dosing guidelines for the 10.0 – 13.9 kg weight bands; 365 days a year

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

No cost-effectiveness analyses for use of RAL were identified.

- **400mg**: WHO's 2016 guidelines recommend replacing the two NRTIs with RAL plus LPV/r as an alternative regimen for second-line treatment in adults. However, as of 2016, the RAL 400mg tablets are significantly more costly than other NRTI backbone options in both the dual fixed-dose combination and single tablets formulations.

- **100mg**: WHO's guidelines recommend RAL plus two NRTIs as an option for second-line treatment in children failing PI-based initial therapy. As of 2016, the RAL tablets are significantly more costly than the LPV/r FDC tablets, but can be an effective drug for young children for whom no other options are available.

- **25mg**: WHO's guidelines recommend RAL plus two NRTIs as an option for second-line treatment in children failing PI-based initial therapy. As of 2016, the RAL tablets are significantly more costly than the LPV/r FDC tablets and LPV/r oral solution, but can be an effective drug for young children for whom no other options are available.

In addition to the cost of the product itself, there are also cost savings related to the shipment and storage of the tablets relative to the oral solution. Due to the oral solution's cold-chain requirements, storage of the tablets is relatively easier. There are also significant freight savings associated with using tablets over oral solutions, which have a significantly greater weight and bulk. Moreover, wastage at the patient level is typically presumed to be significantly higher with oral solutions than tablets.

13. Summary of regulatory status of the medicine

Raltegravir 400 mg tablets (October 2007), 100 mg scored chewable tablets and 25 mg chewable tablets (December 2011) are approved for use in adult and pediatric patients in the U.S. (Merck Sharp & Dohme Corporation) and the E.U. The US FDA granted RAL 400mg tablets (Hetero Lab Ltd) tentative approval in September 2014.

Raltegravir is available in the United States Pharmacopoeia. RAL is not available in the International Pharmacopoeia. The status of RAL in the British pharmacopoeia is unknown, as there was no publicly available version of it available online.

15. Proposed text for WHO model formulary

Dosage forms: 400mg tablet, 100mg scored chewable tablet, 25mg chewable tablet

Description: Raltegravir is an inhibitor of HIV’s integrase enzyme.

Uses: Treatment of HIV in combination with at least two other antiretrovirals in third-line therapy.

Contraindications: Hypersensitivity to RAL or to any of the excipients.

Precautions: Increased serum creatine kinase concentrations have been observed in patients receiving RAL. Myopathy and rhabdomyolysis have been reported rarely, although the relationship to RAL is unknown. Therefore, RAL should be used with caution in patients at increased risk of myopathy or rhabdomyolysis.

Doses: In adults, RAL 400mg BID in combination with at least two other antiretrovirals in third-line therapy.

In children RAL is dosed according to weight as shown in the table as second-line therapy in children failing a PI-containing first regimen.

<table>
<thead>
<tr>
<th>Weight</th>
<th>AM 10.0–13.9 kg</th>
<th>PM 14.0–19.9 kg</th>
<th>AM 20.0–24.9 kg</th>
<th>PM 25.0–34.9 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg chewable</td>
<td>3.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>100 mg chewable</td>
<td>--</td>
<td>--</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>400 mg tablets</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Adverse effects: The most common adverse events reported were insomnia, headache, nausea, asthenia, and fatigue.

Pregnancy: Safety of RAL in pregnant women has not been established.

Drug Interactions Concomitant use with drugs that are strong inducers of uridine diphosphate-glucuronosyltransferase (UGT) 1A1 may result in decreased plasma concentrations of raltegravir. Concomitant use with drugs that are strong inhibitors of UGT 1A1 may result in increased plasma concentrations of raltegravir. Rifampicin is a strong inducer of UGT 1A1. Rifabutin is a weaker inducer and should be considered in this scenario, although both rifamycins have potential to decrease RAL concentrations. If rifampicin is the only available anti-tuberculosis medication available, increasing RAL to 800mg BID should be considered in order to maintain an adequate RAL area under the curve (16). Dosage adjustment of RAL does not appear to be necessary when given with ritonavir boosted atazanavir. Etravirine and efavirenz both decrease serum concentrations of RAL, however the clinical importance is unknown.
WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

References: