Name of the organization supporting the application: Clinton Health Access Initiative (CHAI), Inc

Request: listing is requested on the Model List of Essential Medicines for Children as a new formulation for LPV/r intended for pediatric use; it is an example of the therapeutic class of HIV protease inhibitors. Other members of this class of drugs may serve as alternatives, depending on quality, price and local availability.

(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☒ No ☐

Please provide brief details (in the application):

Lopinavir/ritonavir (LPV/r 40mg/10mg) oral granules are recommended to treat paediatric populations and also to contribute to the UNAIDS goal and global community of ending paediatric HIV by 2020. Infants, young children, and children HIV-infected represent 5% of the total people living with HIV/AIDS globally (around 1.800 million). Despite recognition of the advantages of early treatment, pediatric treatment coverage still only reaches 52% of children eligible for treatment. In 2017 an estimated 110,000 HIV/AIDS related deaths occurred in children <15 years of age. Estimates that around 50% of the children living with HIV worldwide have been receiving ART. The introduction of paediatric ART has changed HIV infection in children from a life-threatening disease into a chronic and manageable disease. Since 2016 WHO Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection, LPV/r-based regimen has been recommended as first-line ART for all children younger than three years.

According to CHAI HIV Market Report, the use of LPV/r in paediatric treatment will remain 25% of the treated children for the next years. The mentioned report notes that since 2016 the demand for LPV/r pellets has outpaced supply. Recent information from Cipla suggests an increasing in the production of LPV/r oral pellets from 20,000 per month to 50,000-60,000 by the end of 2019. LPV/r 100mg oral granules can contribute to ease global supply constraints in the near future. In order to scale-up treatment of paediatric HIV infection, it is critical that ARV dosage forms for use in infant and young children are accessible especially in poor resource settings.
(2) Have all important studies/evidence of which you are aware been included in the application?

Yes ☐ No ☒

Please provide brief comments on any relevant studies that have not been included (not in the application):

At 22nd International AIDS Conference (AIDS 2018) Amsterdam, Netherlands, 23-27 July 2018, researchers from Mylan Laboratories Limited presented the results from a randomized, open-label, balanced, two-treatment, single-dose, crossover oral bioequivalence study of Lopinavir/Ritonavir Oral Granules 40mg/10mg with KALETRA® (Lopinavir/Ritonavir) Oral Solution 80 mg/20mg per mL in healthy adults under fed conditions. The study shows under fed conditions, LPV/r 40/10 mg Granules of Mylan Laboratories Limited, India was bioequivalent to the reference product (R) KALETRA® (LPV/r) Oral Solution 80 mg/20mg per mL, with regard to rate and extent of absorption. The study refers the occurrence of mild adverse effects.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☒ No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine (in the application):

Data supporting effectiveness of LPV/r in adults and children HIV-infected were included in the 2016 dossier that requested the inclusion of LPV/r 40/10mg oral pellets in the EMLc. Applicants assume that LPV/r oral granules are expected to be as effective as LPV/r 40/10 mg oral pellets.

Additionally, the LIVING study, conducted in Kenia and Uganda to evaluate virological outcomes, safety and acceptability of LPV/r 40/10mg oral pellets based-ART in young children which concluded that Naïve children failing NVP, as well as those switching from LPV/r syrup were well suppressed at week 48. LPV/r pellets were well accepted with minimal safety concerns. Based on data provided by the Living Study applicants assume that LPV/r 40/10mg oral granules will also be an effective and acceptable formulation for children.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:
Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes □ No □

Please provide brief details:

The applicant states that LPV/r has been used in paediatric population since its approval in 2000. However, at the moment of the application, there had not been significant use of LPV/r 40/10mg oral granules. Regarding safety, the applicant affirms that in general the safety profile of LPV/r in adults and in children is similar. However, there is limited clinical data on its effectiveness and safety in routine care.

LPV is a potent inhibitor of the CYP3A4 and it is an important drug induced interaction with other medicines metabolized by this isoenzyme.

LPV/r concentration is significantly reduced when is used concomitantly to rifampicin.


Additionally, it is important to consider that the above-mentioned 2018 WHO Guidelines recommends LPV 40/10mg oral pellets or equivalent ‘granules’ formulation to be used in infants and children weighting more than 3 kg.

It also states that solid oral formulations of LPV/r 40/10mg pellets or granules are preferred to LPV/r 80/20ml oral solution, which requires cold chain during transport and storage.

Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Considering the studies presented in the application, the benefit to risk ratio is favourable. The dossier submitted in 2016 requesting addition of the LPV/r pellets to the EMLc summarized data supporting its use. This dossier refers the CHAPAS-2 study – an open-label, randomized, comparative bioavailability trial of LPV/r liquid, pellet and tablet formulations in HIV infected infants and children. In the cohorts of patients aged 3–12 months and 1–4 years, LPV concentrations and pharmacokinetic parameters were slightly higher with pellets than with liquid formulation. For the cohort of older patients (4–<13 years), LPV concentrations were higher with paediatric tablets than with pellets. In the current application more data from LPV/r pellets is available (LIVING study). Based on data provided by the Living Study applicants assume that LPV/r 40/10mg oral granules will also be an effective and acceptable formulation for children, but it is important to observe that there is
currently no experience on the use of LPV/r 40/10mg granules to infants less than 3 months.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☒ No ☐

Please provide brief details (in the application)

Instructions for appropriate use of LPV/r 40/10 mg oral granules are necessary and are described below. Important procedures are necessary to guarantee the full dose administration.

Instructions for mixing LPV/r oral granules (40/10mg):

1. Determine the number of sachet needed to prepare a dose
2. Prior to mix, tap the sachet to move all the granules to the bottom of the sachet(s)
3. Completely tear or cut off the top of the sachet(s) and make sure the sachet(s) are fully open.
4. Mixing with soft food such as applesauce or porridge: using a spoon, mix the entire content of the LPV/r oral granules 40/10mg sachet (1 teaspoon/sachet) in a small cup or bowl. Make sure that no granules are left in the sachet(s). Give or take all the mixture. If any granules are left in the bowl or spoons, add more soft food to the granules and mix. Then give the mixture along with adequate drink water, to ensure that no granules are left behind in the mouth.
5. Mix with liquid such as drinking water: (make sure the drinking water is clear) mix the entire contents of LPV oral granules sachet 40/10mg with approximately 5-15 ml of drinking water in a teaspoon/table spoon (1 teaspoon for 2 sachets...). Make sure that no granules are left in the sachet. Give or take all of the mixture. If granules are left in the spoon add more drinking water and mix. Then give or take the mixture.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☒

Please provide brief details:

FDA granted Mylan’s tentative approval to LPV/r 40mg/10mg oral granules on August 2018. “In May 2004, in support of the President’s Emergency Plan, FDA announced a new initiative to help ensure that those being served by the Presidents’ Plan would receive safe, effective, and quality manufactured
antiretroviral drugs. This new initiative included an expedited review process. FDA reviews the marketing applications using its normal standards for authorization. If the product still has marketing protection in the U.S. FDA issues a "tentative approval" rather than a "full" approval. The "tentative" approval means that the product meets all safety, efficacy, and manufacturing quality standards for marketing in the U.S., and, but for the legal market protection, it would be on the U.S. market. USAID allows, under the President's Emergency Plan, purchase of any product that has either a "full" or "tentative" FDA approval. In this manner, the only products being offered under this program to the focused countries are products that we would offer our own citizens.”

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☒ No ☐

Please provide brief details:

The 2018 WHO Interim Guidelines (WHO2018-CDS-HIV-18.51) recommends the use of the LPV/r 40mg/10mg pellets formulation for infants younger than 3 months or >3-5 kg. Based on this WHO Guidelines proposal of weight-bands, LPV/r 40mg/10mg pellets can be used twice daily dosing in infants >3-5 kg and children up to 24.9 kg.

The 2018 WHO Optimal Formulary (OF-LUL) recommends that as LPV/r solid oral dosage forms are increasingly becoming available and should be used whenever possible; however LPV/r oral liquid may still be required until a solid oral dosage form of LPV/r appropriate for infants aged 2 weeks to 3 months becomes available.

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

According to MSF, July 2018, the average price per patient per year of LPV/r 40mg/10mg oral granules was US$ 281, while the price of LPV/r 40mg/10mg oral pellets was US$ 292 and the price of oral solution US$ 94. Despite being more expensive solid formulations such as pellets and granules are preferred because they are heat stable, which means that they do not require cold chain during transport and storage.

(10) Any additional comments?

(11) Please frame the decisions and recommendations that the Expert Committee could make.

Assuming that both LPV/r 40mg/10mg oral pellets and LPV/r 40mg/10mg oral granules are expected to be similar in effectiveness, acceptability and price, as well as
in order to align with 2018 WHO Interim Guideline and to the WHO Optimal Formulary and Limited Use, the Expert Committee should include LPV/r (40/10mg) oral granules formulation on the EML and the EMLc for treatment of children four weeks of age or more.

Some remarks:

1. Other members of the same class of medicines may serve as alternatives, depending on quality, price and local availability

2. Currently no experience on the use of LPV/r 40/10mg granules to infants less than 3 months is reported.

3. There are differences between Cipla’s LPV 40/10mg pellets (the dosage formulation currently approved in EMLc) and Mylan’s LPV 40/10mg oral granules in terms of packaging and administration.

4. The Antiretroviral Procurement Working Group (APWG) recommends to HIV national programs to adopt only one product to avoid confusion at facilities and for caregivers.

4. The LPV/r 40/10mg formulation may be important in case of LPV/r 40/10 mg oral pellets shortage.

(12) References (not in the application)


https://www.fda.gov/internationalprograms/pepfar/ucm119231.htm