Lopinavir + ritonavir

**Indication**
Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified

**INN**
Lopinavir + ritonavir

**Medicine type**
Chemical agent

**List type**
Core

**Formulations**
- Oral > Liquid: 400 mg + 100 mg per 5 mL
- Oral > Solid: 100 mg + 25 mg tablet (heat-stable) ; 200 mg + 50 mg tablet (heat-stable) (EML) ; 40 mg + 10 mg (EMLc)

**EML status history**
- First added in 2002 (TRS 914)
- Changed in 2007 (TRS 950)
- Changed in 2009 (TRS 958)
- Changed in 2015 (TRS 994)
- Changed in 2017 (TRS 1006)
- Changed in 2019 (TRS 1021)

**Sex**
All

**Age**
Also recommended for children

**Therapeutic alternatives**
The recommendation is for this specific medicine

**Patent information**
Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit [www.MedsPal.org](http://www.MedsPal.org)

**Wikipedia**
Lopinavir + ritonavir

**DrugBank**
Lopinavir, Ritonavir

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**Expert Committee recommendation**
The Expert Committee recommended the addition of a new formulation of lopinavir + ritonavir (LPV/r) oral granules 40 mg + 10 mg fixed-dose combination to the core list of the EMLc for the treatment of children with HIV infection, in line with recommendations in current WHO guidelines, noting the importance of the availability of quality, age-appropriate paediatric dosage forms of antiretroviral medicines. The Committee recommended the new LPV/r oral granules and the existing LPV/r capsules containing oral pellets should be listed collectively as “solid oral dosage form”, for consistency with the the 2018 optimal paediatric ARV formulary.

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**Background**
The application requested addition of a new formulation of lopinavir + ritonavir (LPV/r) fixed-dose combination to the core list of the EMLc for the treatment of children with HIV infection - oral granules, 40 mg + 10 mg. Fixed-dose combinations of LPV/r have been included on the EMLc since 2007. Currently listed formulations are oral liquid 400 mg + 100 mg/5 mL, heat-stable tablets 100 mg + 25 mg and capsules containing oral pellets 40 mg + 10 mg.

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**Public health relevance**
Despite an impressive reduction in mother-to-child transmission of HIV in recent years, 180,000 new paediatric infections occurred in 2017. There are now 1.8 million children living with HIV, the vast majority in sub-Saharan Africa (1). Evidence shows that in the absence of ART, over 50% of HIV-infected infants progress to AIDS and death by the age of 2 years (2), but the introduction of paediatric 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, paediatric treatment coverage still only reaches 52% of children eligible for treatment (1) and in 2017 an estimated 110,000 HIV/AIDS-related deaths occurred in children <15 years of age (3).

**Benefits**

The effectiveness of LPV/r in HIV-infected adult and paediatric patients has been demonstrated in a variety of clinical settings and populations, and has been previously reviewed. The data supporting use of the oral pellets (also LPV/r 40 mg/10 mg) was considered by the Expert Committee in 2017. LPV/r oral granules are expected to be used in the same settings and for the same patient population as the LPV/r pellets. Since the previous EML application for LPV/r pellets was submitted, additional data on this dosage form have been reported. The LIVING Study conducted in Kenya and Uganda evaluated use and acceptability of LPV/r pellets in 723 infants and young children from 3kg to <25kg. As of the July 2018 report, 303 patients had reached week 48 of treatment; 266 had HIV RNA data available for the week 48 visit. At 48 weeks, 49–60% of patients across four age groups had HIV RNA < 50 copies/mL (4). These data suggest that the oral granules will also be an acceptable formulation in young infants. LPV/r oral pellets and oral granules are currently listed as optimal formulations and are listed collectively as a ‘solid oral dosage form 40 mg/10 mg’ on The 2018 optimal formulary and limited-use list for paediatric ARVs (5). These two formulations are listed to be used with two nucleoside reverse transcriptase inhibitors (NRTIs) for alternative first-line or second-line treatment for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole. The optimal paediatric ARV formulary was first developed in 2011 to address this challenge and now provides guidance to streamline the selection of paediatric 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 application also described 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 (6, 7). 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. For patients under 4 years of age, LPV/r pellets were rated by caregivers as being more acceptable than oral solution. In 2016, LPV/r pellets were added to the Optimal List of the Interagency Task Team (IATT) Paediatric ARV Formulary (8). In making this recommendation, the IATT considered that, in resource-limited settings, the LPV/r pellet formulation can offer advantages over LPV/r oral liquid (which is not heat-stable and requires cold-chain transport).

**Harms**

Evidence for the safety of LPV/r in paediatric patients has been previously evaluated. The LPV/r oral granules formulation is expected to have the same safety and tolerability as other LPV/r formulations.

**Additional evidence**

N/A

**Cost / cost effectiveness**

The application reported a price per patient per year (PPPY) for LPV/r oral granules of US$ 281 based on WHO dosing guidelines for the 3 to 9.9kg weight band. This is similar to the PPPY for LPV/r oral pellets, but more expensive than LPV/r oral liquid. It has previously been proposed that cost savings associated with freight and storage are associated with LPV/r oral pellets compared to oral liquid.

**WHO guidelines**

Based on evidence from randomized controlled trials showing the superiority of LPV/r-based regimens over nevirapine (NVP)-based regimens for treating young children, the WHO 2013 guidelines first recommended the use of LPV/r-based treatment in
children younger than 3 years (36 months) of age where feasible, regardless of NNRTI exposure (6). In the WHO 2016 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, LPV/r in combination with two NRTIs is recommended as the preferred regimen in infants and children younger than 3 years (7). The recommended NRTI backbone in this age group is either abacavir (ABC) or zidovudine (ZDV) plus lamivudine (3TC). In the updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV published in 2018, WHO elevated the integrase inhibitors dolutegravir (DTG) and raltegravir (RAL) in combination with two NRTIs to first-line treatment for infants and children (8). However, LPV/r formulations remain alternate first-line treatment in patients younger than 3 years of age and as second-line therapy in older children who have received an integrase inhibitor. Lack of dosing recommendations for young infants (for DTG) and lack of availability (for RAL) of integrase inhibitors will likely mean continued use of LPV/r in young patients for several years.

### Availability

The US FDA granted tentative approval to Mylan’s LPV/r 40 mg/10 mg oral granules in August 2018.

### Other considerations

N/A

8. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendatio