




		EMLc	ATC codes: J05AE03
Indication	Human immunodeficiency virus disease without mention of associated disease or condition, clinical stage unspecified	ICD11 code: 1C62.Z	
INN	Ritonavir		
Medicine type	Chemical agent		
List type	Core		
Formulations	Oral > Liquid: 400 mg per 5 mL Oral > Solid: 25 mg tablet (heat stable) ; 100 mg tablet (heat stable) Oral > Other: 100 mg powder		
EML status history	First added in 2002 (TRS 914) Changed in 2007 (TRS 946) Changed in 2007 (TRS 950) Changed in 2009 (TRS 958) Changed in 2015 (TRS 994) Changed in 2019 (TRS 1021)		
Sex	All		
Age	Also recommended for children		
Therapeutic equivalence	The recommendation is for this specific medicine		
Patent information	Patents have expired in most jurisdictions Read more about patents . 		
Wikipedia	Ritonavir 		
DrugBank	Ritonavir 		

Expert Committee recommendation

The Expert Committee recommended the addition of the new formulation of ritonavir oral powder 100 mg to the core list of the EML and EMLc for the treatment of 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.

Background

Single-agent ritonavir (RTV) has been included on the EMLc since 2007. Currently listed formulations are oral liquid 400 mg/5mL and heat-stable tablets 25 mg and 100 mg. In a separate application to the 2019 Expert Committee, ritonavir oral liquid was proposed for deletion from the EML and EMLc (See 'Other considerations').

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 antiretroviral therapy (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). Children are at particular risk of acquiring TB, although good epidemiologic data has been difficult to collect. A 2016 systematic review and meta-analysis of opportunistic and other infections among HIV-infected children in LMICs confirmed a high incidence rate (12.3% in ART-naive and 8.8% in ART-exposed) of TB co-infection in this population (4). Among children with TB, the WHO estimates that HIV prevalence, in countries with moderate to high prevalence, ranges from 10 to 60% with the variation in rates depending on the background rates of HIV infection (5).

Benefits

RTV is used only for pharmacologic boosting of other protease inhibitors (PI). The amount of RTV used depends on the PI used as the active ARV, but most PIs currently recommended as second- or third-line antiretroviral therapy (ART) require 100 mg of RTV combined with the adult dose of the PI. Paediatric patients may use differing amounts of RTV in boosted PI regimens based on their weight. Evidence supporting the use of RTV as a pharmacologic booster for second- and third-line PIs has previously been accepted by the EML which notes: "Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right." Since 2010, WHO has recommended the approach of 'super-boosting' LPV/r with additional ritonavir (RTV) (1:1 instead of 4:1 LPV/r ratio, i.e. equal doses of LPV and RTV) to manage rifampicin-based TB co-treatment in children on an LPV/r-based regimen (6). Although HIV therapy is life-long, the use of the RTV super-boosted LPV/r regimen is only used for the duration of TB treatment with rifampicin. A retrospective review of ART regimens and outcomes in HIV/TB coinfecting children younger than 2 years in South Africa suggested that super-boosted LPV/r led to better outcomes and less toxicity than earlier PI regimens (7). The adequacy of the super-boosted regimen was confirmed in a pharmacokinetic study conducted in South Africa, which demonstrated that LPV trough concentrations in children receiving super-boosted LPV/r and rifampicin were non-inferior to LPV concentrations in children off TB therapy (8). RTV oral powder is currently listed as a limited use formulation on the optimal paediatric ARV formulary for superboosting of LPV/r during TB co-treatment and boosting non-coformulated PIs (9).

Harms

Evidence for the safety of ritonavir has been considered previously. The adverse event profile of ritonavir observed during paediatric clinical trials has been reported as similar to that for adult patients. Vomiting, diarrhoea and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in greater than or equal to 2% of paediatric patients enrolled in clinical trials. Grade 3–4 laboratory abnormalities occurring in greater than 3% of paediatric patients who received treatment with ritonavir either alone or in combination with reverse transcriptase inhibitors were neutropenia (9%), hyperamylasaemia (7%), thrombocytopenia (5%), anaemia (4%), and elevated aspartate aminotransferase (AST) (3%) (10). The South African retrospective study evaluating PI-based ART in children younger than 2 years of age, also receiving TB treatment, concluded there were only few treatment interruptions due to toxicity. This suggests that the use of boosted LPV/r and TB treatment in this group was generally well tolerated. The authors also noted there were no significant differences in the proportions of children with Grade 3/4 alanine aminotransferase (ALT) elevations in the TB cotreatment groups while receiving TB treatment compared to children on LPV/r alone (7).

Additional evidence

N/A

Cost / cost effectiveness

No cost or cost-effectiveness information is currently publicly available for ritonavir oral powder. The manufacturer has made a general commitment to employ market-specific pricing strategies as part of their commitment to access to medicines (11).

WHO guidelines

WHO guidelines for paediatric HIV treatment recommend the approach of 'super-boosting' LPV/r with additional RTV (1:1 instead of 4:1 LPV/r ratio, i.e. equal doses of LPV and RTV) to manage rifampicin-based TB cotreatment in children on an LPV/r-based regimen (6).

Availability

Ritonavir oral powder is available internationally from Abbvie Inc. Generic brands are not currently available.

Other considerations

In consideration of a separate application requesting the deletion of ritonavir oral liquid from the Model Lists, the Committee recommended that ritonavir oral liquid be retained on the Model Lists at this time. The Committee considered that until the availability is well established of the alternative formulation recommended at this meeting, (i.e. ritonavir 100 mg oral powder), deletion of the existing formulation could be premature. The existing formulation could be flagged for deletion without further discussion in 2021 unless an application is received in support of its retention.

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2. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-inf
3. UNAIDS Core Epidemiology Slides. Geneva: Joint United Nations Programme on HIV/AIDS; 2018. Available from <http://www.unaids.org>
4. B. Lajoie MR, Drouin O, Bartlett G, Nguyen Q, Low A, Gavrilidis G, et al. Incidence and Prevalence of Opportunistic and Other Infections
5. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC Infect Dis. 2018;18(1):1-11.
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8. Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S, et al. Lopinavir-ritonavir super-boosting in young HIV-infected children on antiretroviral therapy. BMC Infect Dis. 2018;18(1):1-11.
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10. U.S. Food and Drug Administration. Norvir package insert, November 15, 2018. Available from: <https://www.accessdata.fda.gov/cdrh/cdrhfiles/nda/2018/021425Orig1s010.pdf>
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