Abacavir + lamivudine + lopinavir + ritonavir

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.2. Antiretrovirals > 6.4.2.5. Fixed-dose combinations of antiretrovirals

EMLc | ATC codes: Pending

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Abacavir + lamivudine + lopinavir + ritonavir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 30 mg + 15 mg + 40 mg + 10 mg capsule containing oral granules (EMLc)
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Abacavir + lamivudine + lopinavir + ritonavir
DrugBank	Abacavir, Lamivudine, Lopinavir, Ritonavir

Expert Committee recommendation

The Expert Committee recognized that age-appropriate, fixed-dose combination formulations of antiretrovirals, when available and quality-assured, are preferred over multiple single-agent formulations to improve treatment adherence and reduce the tablet burden for patients. The Committee noted that dolutegravir, in combination with abacavir and lamivudine, is recommended as the preferred first-line treatment regimen for children with HIV infection in current WHO guidelines, but that abacavir and lamivudine, in combination with lopinavir/ritonavir is an acceptable alternative when dolutegravir-based treatment is not available or appropriate. However, the Committee noted that pharmacokinetic results from the LOLIPOP study indicate that the proposed fixed-dose combination did not meet the criteria for bioequivalence when compared with the reference products, which are currently included on the EMLc. In addition, the Committee noted that the proposed formulation has not yet received regulatory approval from the US Food and Drug Administration. Therefore, the Committee did not recommend inclusion of the fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir on the EMLc.

Background

This formulation had not previously been considered for inclusion on the EMLc. The component medicines are all included on the EMLc in paediatric-friendly formulations.

Public health relevance

HIV infection among children is still a significant problem in developing countries, despite the global progress made in HIV prevention and AIDS treatment. Of the estimated 1.8 million children younger than 15 years living with HIV, 88% live in sub-Saharan Africa and only 53% of the total were receiving antiretroviral therapy by the end of 2019 (1). Many factors contribute to the low treatment coverage for children living with HIV, including challenges unique to children's medicines, diagnosis, case-finding and linkage, and their retention in care (2). Diagnosis of HIV in infants (both early diagnosis and final diagnosis after 18 months) remains poor in many countries, which impedes scaling up treatment for children, especially those younger than 18 months. Even among children who do get onto treatment, retention among children is hindered for many reasons, such as the lack of and sustainable supply of appropriate formulations (3), maintaining a market share for available paediatric formulations and ensuring access in each country (4). Globally in 2019, an estimated 95 000 children younger than 15 years died of AIDS-related causes (1). Without HIV treatment, 50% of infants infected with HIV during or around the time of birth will die by the age of 2 years (4). Many studies have shown that early initiation of antiretroviral therapy in HIV-infected children is associated with clinical and survival benefits (5–11).

Benefits

The phase I/II LOLIPOP study is assessing the pharmacokinetics, safety and acceptability of the fixed-dose combination formulation of abacavir + lamivudine + lopinavir/ritonavir in children living with HIV (12). The 4-in-1 combination (test formulation) was compared with abacavir 60 mg + lamivudine 30 mg (dispersible tablets) + lopinavir/ritonavir 40 mg/10 mg (pellets) (reference formulation) in children infected with HIV and weighing 3–25 kg (inclusive) in Uganda. Study drugs were dosed by WHO weight bands: 3–5.9 kg (weight band 1), 6–9.9 kg (weight band 2), 10–13.9 kg (weight band 3) or 14–19.9 kg (weight band 4). Children in weight bands 2 to 4 were randomly assigned (1:1) by weight band to the reference formulation followed by the test formulation for 21 days each (RT) or to the test formulation followed by reference formulation for 21 days each (TR). Children in weight band 1 only received the test formulation for 21 days. Intensive pharmacokinetic sampling was done after 21 days of treatment with each formulation. Safety was assessed during the whole study period and efficacy at the end of the study. Children's caregivers completed an acceptability questionnaire on the 4-in-1 treatment after 21 days. The application reported interim data on the first 33 enrolled children. Of these, four children were in weight band 1. Of the 29 children in weight bands 2–4, 15 were assigned to RT and 14 were assigned to TR. All children were already on lopinavir/ritonavir therapy and 76% had been on antiretroviral therapy for 6 months or more at the time of enrolment. Most children (88%) had a viral load < 400 copies/mL at baseline. Datasets were available for 31 children. Interim efficacy results showed that the proportion of children with viral load < 400 copies/mL increased from 88% (29/33) at baseline to 97% (30/31) at the end of the study. The proportion with viral load < 50 copies/mL increased from 48% (16/33) to 65% (20/31), when missing data were excluded. The median change in CD4 cell count was +130 (interquartile range (IQR) –398 to +527) and, on average, there was no change in CD4% (IQR –3% to +2%) between baseline and end of the study. Interim pharmacokinetic results showed that with the 4-in-1 formulation, the geometric means for area under the curve 0–12 (AUC0-12) for abacavir, lamivudine, and lopinavir/ritonavir were 5479 ng.h/mL, 6059 ng.h/mL and 88 398 ng.h/mL, respectively. Geometric means for maximum concentration (Cmax) were 1754 ng/mL, 1125 ng/mL and 10 103 ng/mL, respectively. Two children in weight band 1 (with severe wasting secondary to failure to thrive) had lopinavir 12-hour postdose concentration (C12) less than 1000 ng/mL; one remained virally suppressed and one became virally suppressed at the end of the study. Pharmacokinetic results for abacavir showed overlapping exposure curves between the test and reference formulations. The geometric mean ratio was 94% for AUC and 76% for Cmax. The bioequivalence criteria were met for abacavir AUC. Pharmacokinetic results for lamivudine showed the geometric mean ratio was 82% for AUC and 69% for Cmax. Neither AUC nor Cmax met bioequivalence criteria, but were comparable to historical exposures in adults and children. Pharmacokinetic results for lopinavir showed that the geometric mean ratio for AUC was 12%

lower with the test than the reference formulation, with the lower limit of the 90% confidence interval outside the bioequivalence range. For Cmax, the geometric mean ratio was 17% lower with the test formulation. Lopinavir absorption was slower with the test formulation than the reference formulation. Overall, lopinavir exposure was comparable to historical data in adults. Exposure to lopinavir by formulation and weight band showed close to the expected ranges observed in adults for weight bands 2–4. No conclusions could be drawn at this time for weight band 1 because of the small and heterogeneous population in this group. Pharmacokinetic results for ritonavir showed the geometric mean ratio was 87% for AUC and 82% for Cmax.

Harms

The safety of abacavir, lamivudine, and lopinavir/ritonavir as individual medicines has been previously evaluated. From the interim results of the LOLIPOP study, 101 treatment-emergent adverse events were reported, most of which (96%) were mild, and none led to treatment discontinuation. Treatment-emergent adverse events occurred more frequently with the test formulation than the reference formulation (74% versus 56%, respectively) and the same was true for treatment-related adverse events (42% versus 30%). In terms of acceptability, among 31 caregivers interviewed, 97% reported that administering the 4-in-1 formulation was easy or very easy, and 71% reported that the child had no difficulty swallowing it.

Cost / cost effectiveness

The application stated that the proposed fixed-dose combination formulation was not yet marketed, nor was the final price available. The manufacturer, Cipla, has announced an ex-factory price of US$ 15 per pack of 120 capsules. This corresponds to a price per patient per year of US$ 360 for children in weight band 3 (10–13.9 kg). In comparison, the price per patient per year for the component medicines as separate formulations in this weight band is US$ 520.

WHO guidelines

In 2013, WHO guidelines recommended the use of lopinavir/ritonavir-based regimens in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as first-line antiretroviral therapy for all children younger than 3 years infected with HIV, regardless of exposure to non-nucleoside reverse transcriptase inhibitors (13). The 2018 WHO guidelines on treating and preventing HIV infection recommended a dolutegravir-based regimen in combination with abacavir and lamivudine as the preferred first-line regimen for children for whom approved dolutegravir dosing is available (14). In the absence of appropriate dolutegravir formulations and dosing for infants and young children, abacavir and lamivudine in combination with lopinavir/ritonavir is considered an acceptable alternative given the superiority of lopinavir/ritonavir over regimens based on non-nucleoside reverse-transcriptase inhibitors (15). As of 2020, implementation of dolutegravir-based regimens in children has only been feasible for children weighing ≥ 20 kg in whom dolutegravir 50 mg tablets can be used, while children weighing < 20 kg continue to use lopinavir/ritonavir-based regimens (15). Abacavir + lamivudine in combination with lopinavir/ritonavir is still an important alternative regimen for use as first-line treatment for infants and young children (14).

Availability

This formulation does not yet have regulatory approval anywhere in the world. It is currently under review by regulatory authorities in the Democratic Republic of the Congo, Kenya, Malawi, Mozambique, Rwanda, South Africa, Tanzania, Uganda, United States of America (USA), Zambia and Zimbabwe.

Other considerations

Among people with the HLA-B*5701 allele, the use of abacavir can cause fatal hypersensitivity and screening for this allele before starting therapy with abacavir is recommended in Australia, Europe and USA (16). However, data on the prevalence of the HLA-B*5701 allele and usefulness of testing for it among black African children, who comprise most children living with HIV globally, show a low prevalence of the allele (17,18). Furthermore, the

prevalence of adverse events related to abacavir is low, and adverse events occur early in treatment and can be managed. WHO therefore recommends the use of abacavir-based regimens in first- and second-line antiretroviral regimens without the need for testing (19).

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