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F.1 - Abacavir + lamivudine + lopinavir/ritonavir (30 mg + 15 mg + 40mg/10 mg) fixed-dose combination oral granules

MSF strongly supports the proposal of the DNDi for the inclusion of the abacavir + lamivudine + lopinavir/ritonavir (ABC 30 mg + 3TC 15 mg + LPV/r 40mg/10mg) fixed dose combination (FDC) oral granules in the WHO Model List of Essential Medicines for Children, for the treatment of HIV infection among children living with HIV/AIDS.

Abacavir + lamivudine + lopinavir/ritonavir (ABC+3TC+LPV/r) regimen is indicated for treatment of HIV-1 infection in infants and children weighing at least 3 kg, allowing an early antiretroviral treatment in infants and children living with HIV/AIDS and therefore contributing to reduce morbidity and mortality.

Currently, ABC + 3TC scored dispersible tablet FDC (120 mg + 60 mg) and several formulations of LPV/r are included separately in the WHO Model List of Essential Medicines (EML) and in the WHO Model List of Essential Medicines for Children (EMLc).

In 2019, an estimated 95,000 children under 15 years old died of AIDS-related causes. Without antiretroviral treatment, 50% of children living with HIV will die within the two first years of life. Early initiation of antiretroviral therapy is essential in order to reduce the risk of death in early childhood.

The use of LPV/r-based regimens in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) as first-line antiretroviral therapy is recommended for all children younger than 3 years living with HIV/AIDS, since 2013, according to the WHO “Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach”. ABC + 3TC is the preferred NRTI backbone for all infants and children (older than 4 weeks of age) until they reach 20 kg.

According to the 2018 WHO “Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV (interim guidance)”, the evidence of the superiority of dolutegravir (DTG) in adults is extrapolated in making the recommendation to include DTG as the preferred drug for infants and children. The preferred first-line treatment for children is ABC + 3TC + DTG, for children of age and weight groups with approved DTG dosing and ABC + 3TC + LPV/r is the alternative first-line regimen. The preferred second-line treatment for children for whom

non-DTG-based regimens have failed is DTG in combination with 2 NRTIs for children with approved DTG dosing. In case the DTG-based regimen has failed, the preferred second-line regimen should remain 2 NRTIs + LPV/r.

In the 2019 "Update of recommendations on first- and second-line antiretroviral regimens (policy brief)", WHO states that the preferred first-line regimen for children is ABC + 3TC + DTG for age and weight groups with approved DTG dosing and the alternative first-line regimen is ABC + 3TC + LPV/r. This regimen is also one of the alternative second-line regimen for infants and children.

In the 2020 "Considerations for introducing new antiretroviral drug formulations for children: policy brief", WHO states that ABC + 3TC remains the preferred NRTI backbone for all infants and children (older than four weeks of age) and recommends that until a DTG formulation for children weighing less than 20 kg is available, infants and children use LPV/r-containing regimens (superiority of LPV/r over non-nucleoside reverse-transcriptase inhibitor-based regimens). In 2020, country programmes were in the process of introducing or scaling-up LPV/r-based regimens for infants and children weighing less than 20 kg for whom DTG formulations are not yet available.

MSF would like to draw the attention of the Expert Committee to the following points:

- In 2021, country programmes are in the process of preparing the introduction and scale up of dolutegravir 10 mg for children with weight 3 kg or more and age 4 weeks or more. In November 2020, the US Food and Drug Administration (FDA) has granted a tentative approval of dolutegravir 10 mg scored dispersible tablet but this formulation is not widely available yet. Currently, the only formulation listed in the EMLs and widely available is a dolutegravir 50 mg tablet, not a child-friendly formulation and inappropriate for dosing in young children. Therefore, in the settings where appropriate dolutegravir formulations for infants and young children are not available, ABC + 3TC in combination with LPV/r is considered as an important alternative regimen.
- The recently published 2021 WHO "Optimal formulary and limited-use list for antiretroviral drugs for children" recommends ABC + 3TC + LPV/r regimen as an alternative regimen to ABC + 3TC + DTG for infants and children.
- This ABC + 3TC + LPV/r FDC is currently reviewed by the US FDA but has not yet been approved and is not yet commercially available.
- According to the application, dossiers are currently under review by the Regulatory Authorities of Democratic Republic of Congo, Kenya, Malawi, Mozambique, Rwanda, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.
- When ABC + 3TC + LPV/r FDC will be approved by Health authorities and be available, this "4-in-1" FDC would be a useful alternative to DTG-based regimen in

infants, in case of unavailability or intolerance to DTG. This easy-to-use FDC dosage form can reduce the pill burden, simplify supply chain processes and reduce the costs, in comparison with current LPV/r-containing regimens.

- This "4-in-1" FDC will improve significantly the ease of administration for infants and young children: the capsule containing the oral granules allows easy dosing for caregiver, it can be opened and the granules be administered with food (porridge, mashed fruit) or liquids (water, milk), 2 times a day. This formulation presents a strawberry flavour, and could facilitate administration for young children who have challenges with using the currently available LPV/r pellet formulation.
- The inclusion of this "4-in-1" FDC in the EML will serve as a basis for National Essential Medicines lists and therefore will attract additional manufacturers, facilitate importations, alert manufacturers about the need for local registrations, allow for better competition between manufacturers in order to reduce price and improve accessibility, particularly in low- and middle-income countries, and will increase interest for pediatrics formulations.
- Previously, all products in the EMLc were also in the EML: if this logic is maintained, abacavir + lamivudine + lopinavir/ritonavir (30 mg + 15 mg + 40mg/10 mg) FDC oral granules should also be included in the EML.

MSF has been using ABC + 3TC FDC in its programs since 2010, LPV/r formulations since 2004 and the LPV/r 40 mg /10 mg granules pediatric formulation since 2016.

At the end of 2020, in collaboration with Health Authorities in 20 countries, MSF provided antiretroviral treatment for more than 192 000 people living with HIV/AIDS, including 16 800 patients on second-line antiretrovirals.

MSF urges the 23rd Expert Committee on the Selection and Use of Essential Medicines to include abacavir + lamivudine + lopinavir/ritonavir (30 mg + 15 mg + 40 mg/10 mg) fixed dose combination oral granules in the WHO Model List of Essential Medicines for Children and therefore in the WHO Model List of Essential Medicines.

For Médecins Sans Frontières

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