Atazanavir + ritonavir

ATC codes: J05AR23

Indication	Human immunodeficiency virus disease without mention of tuberculosis or malaria, clinical stage unspecified ICD11 code: 1C62.Z
INN	Atazanavir + ritonavir
Medicine type	Diagnostic agent
List type	Core
Formulations	**Oral > Solid:** 300 mg (as sulfate) + 100 mg tablet (heat stable)
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
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 Read more about patents.
Wikipedia	Atazanavir + ritonavir
DrugBank	Atazanavir, Ritonavir

Expert Committee recommendation

The Expert Committee recommended the addition of the fixed-dose combination of atazanavir + ritonavir to the core list of the EML. The Committee noted that ATV/r is recommended in current WHO HIV treatment guidelines as a preferred protease inhibitor for second-line treatment of adults, adolescents and pregnant or breastfeeding women, in combination with a nucleoside reverse transcriptase inhibitor backbone.

Background

Atazanavir 300mg tablets and ritonavir 100mg tablets are both currently included individually on the EML.

Public health relevance

In 2015, there were 36.7 million people living with HIV/AIDS globally, of whom more than 95% were in low- and middle- income countries. There were 2.1 million new HIV-1 infections and 1.1 million HIV-related deaths. Less than half of all infected people were receiving antiretroviral therapy in 2015 (1).

Benefits

Evidence for the clinical effectiveness of atazanavir and ritonavir was evaluated at the time of their individual listings. The application described a recent retrospective study in Nigeria that evaluated virological and

immunological outcomes in patients switched from ritonavir-boosted lopinavir (LPV/r) to an ATV/r-based second-line treatment regimen (2). This study found improvements in immunological responses and no increased risk of virological failure in patients switched from LPV/r- to ATV/r-containing regimens after 24 months of follow-up.

Harms

Evidence for the safety of atazanavir and ritonavir was evaluated at the time of their individual listings. The application described the most common adverse events associated with atazanavir and ritonavir, warnings and precautions, drug interactions and precautions for special populations, with reference to the USA product labels of the two component products.

Additional evidence

Another recent prospective study in high income countries (HIV-CAUSAL Collaboration, 2004–2013) (3) has shown significantly lower mortality, lower incidence of AIDS-defining illness, a greater 12-month increase in CD4 cell count, and a smaller risk of virological failure at 12 months for ritonavir-boosted atazanavir compared with ritonavir-boosted lopinavir. The hazard ratios (HR) for ATZ/r versus LPV/r were significantly lower: HR 0.70 (95% confidence interval (CI) 0.53–0.91) for death; HR 0.67 (95% CI 0.55–0.82) for AIDS-defining illness or death; and HR 0.91 (95% CI 0.84–0.99) for virological failure at 12 months. The mean 12-month increase in CD4 count was 8.15 (95% CI –0.13 to 16.43) cells/mm3 (higher in the ATZ/r group).

Cost / cost effectiveness

The average reported price per patient per year for ATV/r FDC 300 mg/100 mg tablets is US$ 203, compared with US$ 251 for the component medicines supplied separately. The application also claims cost savings associated with the need for fewer packs, and the advantage of simplifying country supply chain management with consolidation around a single FDC product.

WHO guidelines

ATV/r is recommended in the 2016 WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection as one of the preferred protease inhibitors (with LPV/r) for second-line treatment of adults, adolescents and pregnant or breastfeeding women, in combination with an appropriate nucleoside reverse-transcriptase inhibitor (NRTI) backbone (4). A comparative analysis of the characteristics of available ritonavir-boosted protease inhibitors is presented in the guidelines. The advantages of ATV/r compared with LPV/r include the lower pill burden with once daily dosing, and better gastrointestinal tolerability; disadvantages include the incidence of hyperbilirubinaemia and dyslipidaemia and contraindication for patients on rifampicin-containing antituberculosis regimens.

Availability

ATV/r 300-mg (as sulfate)/100-mg tablets are included on WHO’s List of Prequalified Medicinal Products. They are produced by Mylan Laboratories Limited, and Cipla Limited, India.

1. AIDS by the numbers – AIDS is not over, but it can be. Geneva: Joint United Nations Programme on HIV/AIDS; 2016 (http://www.unaids.org/en/resources/documents/2016/AIDS-by-the-numbers, accessed 13 March 2017).
2. Akanmu AS, Adeyemo T, Lesi F, Bello FO, Okwuegbuna K, Oloko K et al. Immunological and virological outcomes of patients switched from LPV/r to ATV/r-containing second-line regimens. Curr HIV Res. 2015;13(3):176–83.
3. Cain LE, Phillips A, Olson A, Sabin C, Jose S, Justice A et al. Boosted lopinavir- versus boosted atazanavir-containing regimens and immunologic, virologic, and clinical outcomes: a prospective study of HIV-infected individuals in high-income countries. Clin Infect Dis. 2015;60(8):1262–8.
4. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 13 March 2017).