Report EVOTAZ® atazanavir/cobicistat

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: atazanavir/cobicistat **Brand Name:** EVOTAZ® **Originator/licensee:** Bristol-Myers Squibb Pharma EEIG **Classification:** NI **ATC code:** J05AR15 **Orphan Status:** **Eu:** No **Us:** No **Mechanism of action:** atazanavir is an azapeptide HIV-1 PI, that selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells. Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat increases the bioavailability and half-life of CYP3A substrates, such as atazanavir [1].	**Authorized Indication:** **EMA:** ATV/co is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults and adolescents (aged ≥12 years weighing at least 35 kg) without known mutations associated with resistance to atazanavir [2]. **FDA:** is a two-drug combination of atazanavir, an HIV-1 protease inhibitor, and cobicistat, a CYP3A inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and paediatric pts weighing at least 35 kg [3]. **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 20/5/2021 **FDA M.A. date:** 31/7/2020 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No --- **ABBREVIATIONS:** **ABC:** abacavir **AE:** Adverse Event **ATV:** atazanavir **ATV/rit:** ritonavir-boosted atazanavir **ATV/co:** cobicistat-boosted atazanavir **BID**: Twice a Day **BR:** Background Regimen **CHMP:** Committee for Medicinal Products for Human Use **COBI**: Cobicistat **DRV:** darunavir **DRV/rit:** ritonavir-boosted darunavir **DRV/co:** cobicistat-boosted darunavir **DTG:** dolutegravir **EVG:** elvitegravir **F/TAF:** emtricitabine/tenofovir alafenamide **FTC:**emtricitabina **M.A.:** Marketing Authorization **NRTIs:** nucleoside reverse transcriptase inhibitors **PI:** protease inhibitor **P.O.:** Positive Opinion **pts:** patients **PK:** pharmacokinetics **QD**: Once a Day **SAEs:** Serious Adverse Events **TAF:** tenofovir alafenamide **TEAEs**: Treatment Emergent Adverse Events **TB:** tuberculosis **URTI**: Upper Respiratory Tract Infections **3TC:** lamivudina	**Summary of clinical EFFICACY:** **GS-US-216-0128 (NCT02016924)***is a phase II/III, multicentric, open-label, multicohort, two-part study evaluating PK, safety, efficacy and antiviral activity of ATV/co or DRV/co administered with a BR in HIV-1 infected, antiretroviral, treatment-experienced, virologically suppressed paediatric pts. Eligible subjects were aged 3 months to <18 years on a stable antiretroviral regimen comprising two NRTIs and either ATV/rit QD or DRV/rit QD or BID for ≥ 3 months prior to screening. The study proceeded in two parts (Part A and Part B), as follows: ● **Part A** (n=79): to evaluate the steady state PK and confirm the dose of ATV/co and DRV/co. Ptswere enrolled sequentially by cohort: Cohort 1: 12 years to <18 years old Cohort 2: 6 years to<18 years old Cohort 3: 3 years to<6 years old Cohort 4: 3 months to <3 years old ● **Part B:** A minimum of 21 additional subjects are planned to be enrolled to evaluate the safety, tolerability and efficacy of the ATV/co or DRV/co regimen. Cohort 1 received 300/150 mg ATV/co (*n*=14) or 800/150 mg DRV/co (*n*=8)orally QD with food and a BR for 48 weeks. The primary efficacy endpoints of this study were: 1) Percentage of subjects with HIV-1 RNA< 50 copies/mL at weeks 12, 24 and 48; 2) Change from baseline in CD4 cell count (cells/µl) and CD4 percentage at weeks 24 and 48, and every 12 weeks after week 48. The rates of virologic suppression (HIV-1 RNA< 50 copies/mL) were 100% at week 12, 64% at week 24 and 93% at week 48 for ATV/co, and high rates of virologic suppression were maintained beyond week 48. There were no clinically relevant changes in CD4 cell counts and CD4 percentage[4-6]. **Although the study is evaluating paediatric pts who are receiving ATV/co or DRV/co, the data submitted focuses on the ATV/co data from the Interim Analysis of Cohort 1 Part A.* **Summary of clinical SAFETY:** AEs were reported for the 93% (13/14) of all subjects treated with ATV/co, the majority of which were grade 1 or 2 in severity and not considered to be related to study drug. Grade 3 AEs were reported for 14.3% of subjects, none of which were considered related to study drug. The three most commonly reported (≥ 20%) AEs in pts treated with ATV /co were: URTI (50%), cough (21%), nasal congestion (21%). AEs considered related to study drug were reported for 29% (4/14) of ATV /co-treated subjects (dyspepsia, hyperbilirubinemia, jaundice, proteinuria, vomiting). No study drug-related AEs with ATV/co were reported in more than one subject each. SAEs were reported for 21% of all ATV/co-treated subjects, and were not considered related to study drug. No deaths were reported [4-6]. **Ongoing studies:** ● ***For the same indication:*** No ● ***For other indications:***Yes **Discontinued studies (for the same indication):** No	**Cost of Therapy** In Italy, the price for 30 tabs of 300/150 mg atazanavir/cobicistat is 616.50 € [7]. **Epidemiology:** In Italy, among 71,204 cases of AIDS reported from 1982 until 2019, just the 1.1% (*n*=812) were paediatric cases: -pts < 13 years at the time of AIDS diagnosis = 758 cases -pts >13 <18 years old, who had acquired the infection vertically = 54 cases [8]. --- **POSSIBLE PLACE IN THERAPY** In pts aged ≥12 years old, Italian guidelines recommend as a first-line therapy: ● Backbone: ABC + 3TC/FTC or TAF + 3TC/FTC; ● 3° drug: ATV/r or DRV/r or DTG or EVG/c. The second-line therapy consists of: ● Backbone: ZDV+3TC or ABC+ 3TC or TAF+3TC/FTC; ● 3° drug: LPV/r or RAL or DRV/co [9]. **OTHER INDICATIONS IN DEVELOPMENT:** No **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** Yes (NCT01108510) [10]. **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Doravirine/Islatravir [11]. *Service reorganization Y/N No *Possible off label use Y/N Yes --- **References:** 1. https://www.ema.europa.eu/en/documents/product-nformation/evotaz-epar-product-information_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/evotaz-0 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/206353s007lbl.pdf 4. https://adisinsight.springer.com/trials/700240640 5.https://www.ema.europa.eu/en/documents/variation-report/evotaz-h-c-003904-ii-0038-epar-assessment-report-variation_en.pdf 6.https://2jg4quetidw2blbbq2ixwziw-wpengine.netdna-ssl.com/wp-content/uploads/sites/2/posters/2017/425_Kido.pdf 7. https://gallery.farmadati.it/Home.aspx 8.https://www.salute.gov.it/imgs/C_17_pubblicazioni_2979_allegato.pdf 9.https://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf 10. https://adisinsight.springer.com/trials/700055741 11.https://clinicaltrials.gov/ct2/show/NCT04295772?recrs=abdf&type=Intr&cond=HIV-1-infection&age=01&phase=12&draw=2&rank=2

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