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Committee for Medicinal Products for Human Use (CHMP)

Viread

(tenofovir disoproxil fumarate)

Procedure No. EMEA/H/C/000419/P46/249

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. INTRODUCTION

In accordance with Article 46 of Regulation (EC) No 1901/2006, Gilead Sciences International Limited (GSIL) submitted to the EMA a 72 week interim report for Study GS-US-174-0115, '*A Randomised, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection*.'

In December 2011, GILEAD is planning to submit a Type II variation that will seek to register a new paediatric indication for Viread for the treatment of adolescents with chronic hepatitis B. This will be based on the pivotal 72 week data presented in this 'Article 46' submission.

GILEAD stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for Viread 245 mg film-coated tablets and therefore no further regulatory action is required on the marketing authorisation for Viread 245 mg film-coated tablets at this time.

2. SCIENTIFIC DISCUSSION

Study GS-US-174-0115 consists of an initial 72 weeks of randomized, double-blind treatment with TDF 300 mg or PLB once daily, followed by open-label TDF treatment, for up to a total of 4 years (through Week 192). Subjects enrolled in this study (n=106) were TDF-naive adolescents (12 to 17 years of age) with HBeAg+ or HBeAg− compensated CHB, and included both HBV-treatment experienced and treatment-naive subjects.
The primary efficacy endpoint was HBV DNA < 400 copies/mL at Week 72.

Risk-benefit evaluation supported use of a blinded study design using placebo (PLB) for 72 weeks as an appropriate comparator. Use of the PLB comparator allowed a more robust evaluation of TDF safety and tolerability (e.g., bone metabolism, renal safety), and did not expose subjects randomized to the PLB group to the theoretical risk of developing resistance to TDF during the blinded portion of the study. Furthermore, during the open-label period, subjects randomized to PLB are given open-label TDF which affords them access to active HBV treatment and allows for assessment of changes in safety and tolerability (e.g. bone metabolism, renal safety) in subjects commencing TDF treatment at Week 72

GS-US-174-0115: Overview of Study

Study (Module 5 Reference)	Design	Geographic Location	Study Population	Treatment	Subjects Treated	Duration (Status)
GS-US-174-0115 (m5.3.5.1)	Randomized, double-blind, placebo-controlled, multicenter, Phase 3 study in HBV-infected adolescent subjects	Poland (8 sites), Romania (3), United States (3), Bulgaria (2), France (2), Spain (2), and Turkey (1)	TDF-naïve adolescent subjects (12 to 17 years of age) with chronic HBeAg-positive or HBeAg negative HBV infection	TDF 300-mg tablets once daily or placebo (PLB) tablets once daily	Week 72: 106 subjects: 52 TDF and 54 PLB	192 weeks (ongoing); 72-week randomized period completed

TDF (300-mg once daily) therapy in HBV-infected adolescents results in highly effective suppression of HBV DNA (84.6%. had HBV DNA <169 copies/mL at Week 72 versus 0% in placebo arm), normalization of ALT, and suppression of hepatic flares, even among adolescents with prior exposure to HBV therapies.

The safety profile in adolescent subjects with chronic HBV infection treated with TDF was generally consistent with the known safety profile of TDF in adults with HBV. However, the percent increase from BL in lumbar spine BMD in TDF-treated subjects was less than the percent increase in lumbar spine BMD attained by PLB-treated subjects (4.95% in the TDF group vs. 8.14% in the PLB group, by Week 72).

3. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

In accordance with Article 46 of Regulation (EC) No 1901/2006, Gilead submitted the 72 week interim report for Study GS-US-174-0115, 'A Randomised, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection.'

Similarly to adults, VIREAD seems to be a potent drug in HBV-infected adolescents. The safety aspects, notably the impact on bone, will be the salient issue to be discussed in the benefit/risk assessment of use of VIREAD in HBV-infected adolescents.

No benefit/risk evaluation is made at this stage. A full benefit/risk assessment will be made in the frame of the upcoming type II variation procedure scheduled for submission in December 2011.

Recommendation

☒ **Fulfilled**