PASS Information

Study Title	An Observational, Drug Utilization Study of Viread in Children and Adolescents with HIV-1 Infection
Version identifier of the interim study report	GS-EU-104-0433 Final
Date of last version of the interim study report	December 2016
EU PAS register number	ENCEPP/SDPP/7814
Active substance	ATC Code: J05AF07 Antiviral for systemic use: Nucleoside and nucleotide reverse transcriptase inhibitors Active substance: Tenofovir disoproxil fumarate
Medicinal product	Viread
Product reference	Viread
Procedure number	EU/1/01/200/001-009
Marketing authorization holder	Gilead Sciences International Ltd Cambridge, United Kingdom CB21 6GT
Joint PASS	No
Research question and objectives	To describe the characteristics of HIV-1 infected patients up to 18 years of age treated with either Viread or TDF-FDC within the EU and to examine the usage of Viread in order to determine if patients are being managed in accordance with the European SmPC.
Country (-ies) of study	European Union member states that participate in the European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) pharmacovigilance programme

Authors

PPD
Gilead Sciences International, Ltd
Telephone:+PPD

PPD

PPD

PPD

Direct line: PPD
Main switchboard: PPD

Gilead EU QPPV:

PPD

Telephone: PPD
Fax: PPD

Marketing authorisation holder(s)

Gilead Sciences International Ltd
Cambridge, United Kingdom
CB21 6GT

MAH contact person

PPD
Telephone: PPD
E-mail: PPD

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF IN-TEXT FIGURES

1. ABSTRACT

Title

An Observational, Drug Utilization Study of Viread in Children and Adolescents with HIV-1 Infection

Keywords

Retrospective cohort study, Drug Utilization, GS-EU-104-0433, Viread, Stribild, Eviplera, Truvada, Atripla, pediatric

Rationale and background

On 22 November 2012 the European Commission adopted a Decision on applications to extend the indications for Viread to include children and adolescent patients with HIV-1 infection aged 2 to < 18 years and adolescents with chronic hepatitis B (CHB) infection aged 12 to < 18 years.

The Summary of Product Characteristics (SmPC) updated in November 2012 for the different formulations of Viread contains information relevant to prescribers of pediatric patients, including the approved indications and appropriate doses of Viread, and recommendations on monitoring of renal function and management of renal and bone abnormalities.

In addition, an educational brochure specific to the use of Viread in children and adolescents with HIV-1 infection was developed for use by prescribers of HIV-1 infected pediatric patients as a risk minimization tool.

In Europe, several established, prospective observational cohort studies of HIV-1 infected children and adolescents participate in the European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC). Gilead Sciences has initiated a collaboration with EPPICC to design a Drug Utilization Study using these cohorts of HIV-1 infected children living in the EU.

The rationale for this study was initially to assess characteristics of pediatric patients treated with Viread prior to and following the approval of the pediatric indication on 22 November 2012, and to assess how physicians are prescribing Viread to children and adolescents, including off-label use in the 0 to < 2 years group, in order to determine the effectiveness of the risk minimization measures i.e. the SmPC and the educational brochure.

Following the 2015 data merger in support of the GS-EU-104-0433 first interim report it became apparent that there were large numbers of children and adolescents receiving tenofovir disoproxil fumarate-containing fixed dose combinations which were not approved for pediatric use in Europe at that time. Data on the characteristics of these patients were reported as part of a Supplementary report in March 2016. Following the recommendations of the Rapporteur, description of the characteristics of this population, the renal and bone monitoring following

initiation of these regimens and adverse events have been added as a secondary objective to this study.

Research question and objectives

The primary objectives of this study were:

To describe the characteristics of HIV-1 infected patients < 18 years of age being treated with Viread by collection of the following:

- Appropriateness of dose of Viread for the patients' age and weight
- Prior antiretroviral therapy (ART) before starting Viread therapy
- Documented evaluation of renal function (creatinine clearance and serum phosphate) prior to initiating Viread and during Viread therapy

To assess the clinical management and outcome of any ≥ Grade 3 renal and bone biochemistry markers, confirmed serum phosphate values of < 3.0 mg/dl (0.96 mmol/l) in the post approval group and serious adverse drug reactions in patients receiving Viread in order to determine if they are being managed in accordance with the European SmPC

To compare the characteristics of HIV-1 infected patients less than 18 years of age receiving Viread, at and each year after, the approval of the pediatric indication for Viread

The secondary objectives of this study are:

To evaluate and describe the characteristics of HIV-1 infected patients < 18 years of age being treated with tenofovir disoproxil fumarate (TDF)-based regimens (including off-label use of TDF-containing fixed dose combination (FDC)) at or after the Viread approval date by collection of the following variables:

- Prior antiretroviral treatment (ART)
- First TDF-based regimen
- Initiation of TDF-FDC at or after the Viread approval date for the treatment of HIV-1 infected patients aged 2 to <18 years of age

To assess the monitoring and outcome of any ≥ Grade 3 renal and bone biochemistry markers and serious adverse drug reactions in patients receiving TDF-FDC.

Study design

Pooled analysis of anonymised individual patient data for cohorts participating in the European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) pharmacovigilance programme

was conducted for children treated with Viread or TDF-FDC at or after the Viread approval date (22nd November 2012).

Study Population

The study population comprised HIV-1 infected children and adolescents less than 18 years of age (including those under 2 years as off-label use) taking Viread and/or TDF-FDC in the EU on or after 22nd November 2012. The data were collected by annual pooling of anonymised individual patient data in EU–based cohorts participating in EPPICC. Patients in cohorts were followed up until they transferred to adult care, the median age of which varies by country.

Study size

The EPPICC cohorts estimated that 250 patients who have taken Viread pre-approval and continued on Viread post-approval or who have commenced Viread post-approval would contribute to the 2017 merger. The report also includes approximately 750 patients who have taken TDF-FDC prior to or after the Viread approval date.

Variables and data sources

Variables collected on all children taking Viread or TDF-FDC include: basic demographic details (date of birth, sex, mode of infection, ethnicity, hepatitis B and hepatitis C co-infection status); patient weights and heights at every clinic visit; ART dosing history, including reasons for stopping a drug; renal and bone serum chemistries (actual values); all serious clinical adverse events and all non-serious clinical events considered to be causally related to Viread or TDF-FDC exposure (both coded using MedDRA). All events meeting DAIDS grade 3 and 4 renal and bone biochemistry markers while on Viread or TDF FDC were also collected.

Additional data were collected on children taking Viread post approval who experienced a Grade 3 or greater renal or bone laboratory results or confirmed serum phosphate values of < 3.0 mg/dl (0.96 mmol/l) and these comprised: the outcome of the event (resolved versus continuing); whether Viread was discontinued; consultation with endocrinologist/ nephrologist; concomitant medication at the time of the event, and use of dietary supplementation.

Results

This third and final data merger includes retrospectively collected data up to January 2017 (last date of data inclusion) from 13 cohorts across 12 countries in the European Union.

The number of children who received Viread on or post-approval increased from 208 reported in 2016 to 253 in 2017. Similarly, the numbers of patients who received TDF-FDC on or after the Viread approval date increased from 647 to 745. The majority of children on a TDF-FDC received either Truvada (451 subjects) or Atripla (253 subjects). A smaller number of patients received Eviplera (34 subjects) and even fewer received Stribild (7 subjects). Across all TDF-based regimens the overall increase in patients is principally associated with patients initiating Truvada since the last data merger in 2016. For this third year report, which includes new and updated data from a data merger conducted between January and March 2017, the

EPPICC data demonstrate that Viread is prescribed in a number of countries within the EU to treat the pediatric HIV population. The data suggest that monitoring of renal and bone function before and after initiation of Viread has generally improved in patients who initiated Viread in the post-approval versus the pre-approval period. No appreciable changes in monitoring were expected between the 2016 and 2017 data mergers.

Summaries of monitoring practices describe the proportion of children who received renal and bone monitoring ≤30 days and within 6 months before initiation of Viread and ≤3 months after start of treatment. Approximately 25% of patients received serum phosphate and serum calcium assessments (52 and 60 patients, respectively), and 38% received serum creatinine assessments (87 patients) ≤30 days before Viread initiation and were higher if the window was extended to 6 months prior to Viread initiation; a higher proportion of patients received renal (55% serum creatinine and 39% serum phosphate, 125 and 89 patients, respectively) and bone monitoring (39% serum calcium, 88 patients) within ≤3 months after the start of Viread. These proportions have remained stable across the prior study reporting periods. Monitoring improved in patients who initiated Viread post-approval (47%, 36 patients) when compared to the pre-approval group (30%, 45 patients); serum creatinine was measured in 49% of patients in the pre-approval group (73 patients) and increased to 68% of patients (52 patients) who initiated Viread post approval. Fewer patients initiated Viread after its approval than prior to its approval. Laboratory monitoring after starting Viread appeared to be consistent with a median of three months between each of the selected serum renal and bone measures in both the pre-approval and the post-approval groups. Similar trends were observed in those receiving TDF-FDC.

Overall, safety events related to DAIDS Grade 3 or 4 laboratory results remained infrequent. Of the 62 patients with available laboratory data and taking a licensed dose of Viread prior to the approval in children, there was a single Grade 3 serum creatinine laboratory event among 303 person years of Viread exposure. There were six DAIDS Grade 3 serum phosphate events and one serum calcium event (over 262 and 282 person-years of Viread exposure, respectively). Five of the six Grade 3 phosphate events were reported after 24 months of Viread treatment. Five of the six patients did not discontinue Viread treatment and represented no change from last year's report based on the 2016 data merger. No new laboratory Grade 3 phosphate, calcium, or serum creatinine events in patients who initiated Viread were observed since the second data merger took place. There continued to be no Grade 3 or greater renal or bone biochemistry marker outcomes reported among pediatric patients initiating Viread in the post-approval period, whether on a licensed or unlicensed dose and therefore no follow-up inquiries related to clinical management or medical consults occurred.

The majority of possible and probable clinical adverse reactions while on Viread were previously reported in the 2016 interim report. New events among the 253 patients initiated on Viread with available clinical data, included one patient in the pre-approval Viread licensed dose group with low phosphate. In the post-approval licensed dose group there were five new non-serious clinical adverse events (i.e. changes in Vitamin D levels, elevated creatinine, unspecified renal changes, proteinuria, and nausea), three of which resolved and Viread continued in all cases except for two where unrelated factors led to drug discontinuation.

Adherence to SmPC dosing guidance was not consistently followed among patients who initiated Viread prior to the pediatric indication being granted by the EU; however, in the post-approval period, the majority of patients (64%) were on a licensed dose, 8% were on an unlicensed dose, while 28% had missing weight/dose data and therefore could not be assessed for dose appropriateness. Five children under the age of 2 (all from the UK/Ireland cohort) had been previously reported as having received Viread in the pre-approval period only and the dosages unknown.

Trends observed with the Viread treatment group were reflected in children treated with off-label use of TDF-FDC. The most common regimens in use are Truvada and Atripla, which are HIV medicines that have been commercially available in the EU longer than the other TDF-FDC medicines, Eviplera and Stribild. While children prescribed TDF-FDC continue to be treatment experienced as with patients commencing Viread, the median age at start of TDF-FDC was older (13.8 years [IQR 12.0, 15.3 years]) than those initiating Viread (10.5 years [IQR 7.7, 13.6 years]). Monitoring of renal and bone biochemistry was infrequent with just over half of patients monitored for creatinine and less frequent monitoring of phosphate and calcium within 3 months after start of TDF FDC. As TDF-FDCs were off-label in their use in pediatrics there was no SmPC to guide treatment or monitoring practices in children. The nature and frequency of laboratory and clinical adverse drug reactions were not dissimilar to those on Viread; the number of bone and renal adverse outcomes was infrequent and similar to that for Viread. Fewer patients had discontinued TDF-FDC (16%, 118 patients) at last follow up as compared with Viread (32%, 82 patients). Among those who discontinued the drug, the majority of patients on Viread or TDF-FDC completed at least one year of treatment before discontinuation. For patients who discontinued the drug, 37% of patients (30 patients) on Viread cited a desire to move to a simplified treatment, compared to only 19% of TDF-FDC patients (22 patients) who cited the same reason for discontinuation. Despite prevalent off-label use of TDF-FDC in the EPPICC cohorts, there has been no concerning trend in renal and bone safety outcomes and is reflective to what was observed with Viread exposure and it appears that some patients opt for a FDC regimen to achieve simplified treatment. Neither Viread nor TDF-FDC exposed groups fully adhered to monitoring guidelines for renal or bone changes before and after treatment initiation; however, reported renal and bone adverse events were infrequent.

Discussion

The report characterizes both Viread and TDF-FDC for the treatment of HIV-1 among pediatric populations aged less than eighteen years of age at start of treatment. Compared to the second data merger which reported 208 children on Viread, this year the cumulative number rose to 253; however, a much larger number were taking TDF-FDC and rose from 341 patients (to 2015) to 745 in 2017, despite these formulations not having approval for use in children at the time of the data merger. Simplified regimens, which may include switching to single tablet HIV regimens, may be a significant driver in the long term management of HIV. Until dosing SmPC recommendations were issued with the approval of Viread, 16% of pediatric patients (26 of 163 patients) initiated on what became unlicensed doses of the drug. This pattern appears to have been ameliorated in the post-approval period, where 8% of patients (7 of 90 patients) were on an off-label dose.

The majority of children initiating Viread were treatment-experienced (89%) and treated with ART for several years (median 6.6 [2.3-10.0] years) before taking Viread. DAIDS Grade 3 or 4 renal (serum creatinine and phosphate) and bone (calcium) laboratory adverse events, were very infrequent, ranging from 0 to 6 events over patients' cumulative time in the EPPICC cohort. Outcomes related to the detection of laboratory adverse events showed that most events resolved without a need to discontinue the use of Viread. As with the 2016 data merger, there were few new adverse events reported this year. No events met the criteria for the assessment of the clinical management and outcome of any ≥ Grade 3 renal and bone biochemistry markers and confirmed serum phosphate values of < 3.0mg/dl (0.96 mmol/l) in the post approval group receiving Viread. The proportion with tests within 30 days up to six months before starting Viread/TDF-FDC and ≤3 months after start were lower than expected but did improve in those starting Viread post approval and was highest for creatinine monitoring. Also there were wide variations across the countries which may reflect differences in local practice/resources available. Renal and bone monitoring occurred less frequently than expected by the guidance in the Viread SmPC but significant renal and bone related events were infrequent. With data in some patients extending back to almost a decade of exposure to Viread, the observational EPPICC cohort data (2014-2017) did not signal any trends toward renal or bone safety concerns in children and overall, provides support for safe long term use of the TDF-containing medicines for the treatment of HIV-1.

Names and affiliations of principal investigators

PPD
PPD
PPD

PPD
PPD