EMA/65153/2022

European Medicines Agency decision

P/0073/2022

of 11 March 2022

on the acceptance of a modification of an agreed paediatric investigation plan for tenofovir disoproxil (Viread), (EMEA-000533-PIP01-08-M11) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/18/2010 issued on 8 February 2010, decision P/51/2011 issued on 4 March 2011, decision P/180/2011 issued on 28 July 2011, decision P/0109/2012 issued on 8 June 2012, decision P/0018/2013 issued on 31 January 2013, decision P/0249/2014 issued on 30 September 2014, decision P/0192/2015 issued on 4 September 2015, decision P/0262/2017 issued on 4 September 2017, decision P/0121/2020 issued on 20 March 2020, decision P/0437/2020 of 20 November 2020 and decision P/0156/2021 on 14 April 2021,

Having regard to the application submitted by Gilead Sciences International Limited on 8 October 2021 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 21 January 2022, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to the agreed paediatric investigation plan.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[1] OJ L 378, 27.12.2006, p.1, as amended.
[2] OJ L 136, 30.4.2004, p. 1, as amended.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for tenofovir disoproxil (Viread), film-coated tablet, granules, oral use, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to Gilead Sciences International Limited, Granta Park, CB21 6GT – Cambridge, United Kingdom.

EMA/PDCO/579161/2021
Amsterdam, 21 January 2022

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-000533-PIP01-08-M11

Scope of the application

Active substance(s):

Tenofovir disoproxil

Invented name:

Viread

Condition(s):

Treatment of human immunodeficiency virus (HIV-1) infection

Treatment of chronic viral hepatitis B

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Granules

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Gilead Sciences International Limited

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Gilead Sciences International Limited submitted to the European Medicines Agency on 8 October 2021 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/18/2010 issued on 8 February 2010, decision P/51/2011 issued on 4 March 2011, decision P/180/2011 issued on 28 July 2011, decision P/0109/2012 issued on 8 June 2012, decision P/0018/2013 issued on 31 January 2013, decision P/0249/2014 issued on 30 September 2014, decision P/0192/2015 issued on 4 September 2015, decision P/0262/2017 issued on 4 September 2017, decision P/0121/2020 issued on 20 March 2020, decision P/0437/2020 of 20 November 2020 and decision P/0156/2021 on 14 April 2021.

The application for modification proposed changes to the agreed paediatric investigation plan.

The procedure started on 22 November 2021.

Scope of the modification

Some measures of the Paediatric Investigation Plan have been modified.

Opinion

The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion;

The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

The measures and timelines of the paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annexes and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

1. Waiver

1.1. Condition:

Treatment of human immunodeficiency virus (HIV-1) infection

The waiver applies to:

- infants and toddlers from birth to less than 2 years of age;
- film-coated tablet, granules, oral use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

1.2. Condition:

Treatment of chronic viral hepatitis B

The waiver applies to:

- infants and toddlers from birth to less than 2 years of age;
- film-coated tablet, granules, oral use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

2. Paediatric investigation plan

2.1. Condition:

Treatment of human immunodeficiency virus (HIV-1) infection

2.1.1. Indication(s) targeted by the PIP

In combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in antiretroviral treatment experienced paediatric patients

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From 2 to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Film-coated tablet

Granules (considered identical with the oral powder used in the United States)

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable
Non-clinical studies	0	Not applicable
Clinical studies	2	**Study 1: GS-US-104-0321** Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1-Infected Adolescents. **Study 2: GS-US- 104-0352** Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy. **Study 3** Deleted in EMEA-000533-PIP01-08-M07
Extrapolation, modelling and simulation studies	0	Not applicable
Other studies	0	Not applicable
Other measures	0	Not applicable

2.2. Condition:

Treatment of chronic viral hepatitis B

2.2.1. Indication(s) targeted by the PIP

For treatment of chronic hepatitis B in paediatric patients from 2 years of age with compensated liver disease.

2.2.2. Subset(s) of the paediatric population concerned by the paediatric development

From 2 to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Film-coated tablet

Granules (considered identical with the oral powder used in the United States)

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable
Non-clinical studies	0	Not applicable
Clinical studies	2	**Study 4: GS-US-174-0115.** A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection. **Study 5:** A safety and efficacy or pharmacokinetic study of tenofovir DF in children aged 2 to < 12 years with chronic HBV infection. **Study 6:** (deleted during EMEA-000533-PIP01-08-M10)
Extrapolation, modelling and simulation studies	0	Not applicable
Other studies	0	Not applicable
Other measures	0	Not applicable

3. Follow-up, completion and deferral of PIP

Concerns on potential long-term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By June 2020
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

Treatment of human immunodeficiency virus (HIV-1) infection

Authorised indication(s):

Viread 123 mg film coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected paediatric patients, with NRTI resistance or toxicities precluding the use of first line agents, aged 6 to < 12 years who weigh from 17 kg to less than 22 kg.

The choice of Viread to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Viread 163 mg film coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected paediatric patients, with NRTI resistance or toxicities precluding the use of first line agents, aged 6 to < 12 years who weigh from 22 kg to less than 28 kg.

The choice of Viread to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Viread 204 mg film coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected paediatric patients, with NRTI resistance or toxicities precluding the use of first line agents, aged 6 to < 12 years who weigh from 28 kg to less than 35 kg.

The choice of Viread to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Viread 245 mg film coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected adults.

In adults, the demonstration of the benefit of Viread in HIV 1 infection is based on results of one study in treatment naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which Viread was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).

Viread 245 mg film coated tablets are also indicated for the treatment of HIV 1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

The choice of Viread to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Viread 33 mg/g granules are indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected paediatric patients, with NRTI resistance or toxicities precluding the use of first line agents, from 2 to < 6 years of age, and above 6 years of age for whom a solid dosage form is not appropriate.

Viread 33 mg/g granules are also indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected adults for whom a solid dosage form is not appropriate.

In adults, the demonstration of the benefit of Viread in HIV 1 infection is based on results of one study in treatment naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which Viread was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).

The choice of Viread to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Treatment of chronic viral hepatitis B

Authorised indication(s):

Viread 123 mg film coated tablets are indicated for the treatment of chronic hepatitis B in paediatric patients aged 6 to < 12 years who weigh from 17 kg to less than 22 kg, with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, 4.8 and 5.1.

Viread 163 mg film coated tablets are indicated for the treatment of chronic hepatitis B in paediatric patients aged 6 to < 12 years who weigh from 22 kg to less than 28 kg, with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, 4.8 and 5.1.

Viread 204 mg film coated tablets are indicated for the treatment of chronic hepatitis B in paediatric patients aged 6 to < 12 years who weigh from 28 kg to less than 35 kg, with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, 4.8 and 5.1.

Viread 245 mg film coated tablets are indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).
- evidence of lamivudine resistant hepatitis B virus (see sections 4.8 and 5.1).
- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

Viread 245 mg film coated tablets are indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, 4.8 and 5.1.

Viread 33 mg/g granules are indicated for the treatment of chronic hepatitis B in adults for whom a solid dosage form is not appropriate with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).

- evidence of lamivudine resistant hepatitis B virus (see sections 4.8 and 5.1).
- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

Viread 33 mg/g granules are also indicated for the treatment of chronic hepatitis B in paediatric patients 2 to < 18 years of age for whom a solid dosage form is not appropriate with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication, and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, 4.8 and 5.1.

Authorised pharmaceutical form(s):

Film-coated tablet

Granules

Authorised route(s) of administration:

Oral use