EMA/530860/2015

European Medicines Agency decision

P/0192/2015

of 4 September 2015

on the acceptance of a modification of an agreed paediatric investigation plan for tenofovir (disoproxil fumarate) (Viread) (EMEA-000533-PIP01-08-M06) 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 Community procedures for the authorisation and supervision of medicinal products for human and veterinary 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, the decision P/51/2011 issued on 4 March 2011, the decision P/180/2011 issued on 28 July 2011, the decision P/0109/2012 issued on 8 June 2012, the decision P/0018/2013 issued on 31 January 2013, and the decision P/0249/2014 issued on 30 September 2014,

Having regard to the application submitted by Gilead Sciences International Ltd on 24 April 2015 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 17 July 2015, 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 and to the deferral.

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

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

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for tenofovir (disoproxil fumarate) (Viread), film-coated tablet , granules, oral use, including changes to the deferral, 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 Ltd, Granta Park, Abington, CB21 6GT – Cambridge, United Kingdom.

Done at London, 4 September 2015

For the European Medicines Agency
Jordi Llinares Garcia
Head of Division (ad interim)
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/304497/2015
London, 17 July 2015

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

EMEA-000533-PIP01-08-M06

Scope of the application

Active substance(s):

Tenofovir (disoproxil fumarate)

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 Ltd

Information about the authorised medicinal product:

See Annex II

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Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Gilead Sciences International Ltd submitted to the European Medicines Agency on 24 April 2015 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, the decision P/51/2011 issued on 4 March 2011, the decision P/180/2011 issued on 28 July 2011, the decision P/0109/2012 issued on 8 June 2012, the decision P/0018/2013 issued on 31 January 2013, and the decision P/0249/2014 issued on 30 September 2014.

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

The procedure started on 19 May 2015.

Scope of the modification

Some timelines of the Paediatric Investigation Plan have been modified.

Opinion

1. 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 and to the deferral 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.

2. 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:

- children from birth to less than 12 years of age;
- for tenofovir DF film-coated tablet for oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

1.2. Condition:

Treatment of chronic viral hepatitis B

The waiver applies to:

- children from birth to less than 12 years;
- for tenofovir DF film-coated tablet for oral use;
- on the grounds that the specific medicinal product is likely to be unsafe.

The waiver applies to:

- infants and toddlers from birth to less than 2 years;
- for tenofovir DF granules;
- on the grounds that clinical studies cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population.

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

1. The paediatric population from 12 years to less than 18 years of age for the film-coated tablets for oral use.
2. All subsets of the paediatric population from birth to less than 18 years of age for the granules.

2.1.3. Pharmaceutical form(s)

Film-coated tablet

Granules (considered identical with the oral powder used in the USA)

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable.
Non-clinical studies	0	Not applicable.
Clinical studies	3	**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:** A safety and pharmacokinetic study of tenofovir DF oral powder in HIV-1 infected subjects < 2 years of age.
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

1. The paediatric population from 12 years to less than 18 years of age for the film-coated tablets for oral use.
2. All subsets of the paediatric population from 2 years to less than 18 years of age for the granules.

2.2.3. Pharmaceutical form(s)

Film-coated tablet

Granules (considered identical with the oral powder used in the USA)

2.2.4. Measures

Area	Number of measures	Description
Quality-related studies		Not applicable.
Non-clinical studies		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:** Randomised open label multicentre study to evaluate efficacy and safety, of tenofovir in children and adolescents with decompensated chronic hepatitis B virus infection in patients aged from 2 to less than 18 years.
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 2021
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):

1. Treatment of human immunodeficiency virus (HIV-1) infection

Authorised indication(s):

- 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.
- 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.
- 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.
- 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.
- 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.

2. Treatment of chronic viral hepatitis B

Authorised indication(s):

- 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, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis (see sections 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 adolescents 12 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, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis (see sections 4.4, 4.8 and 5.1).

Authorised pharmaceutical form(s):

Film-coated tablet, granules

Authorised route(s) of administration:

Oral use