Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tivicay and Tivicay PD

Active ingredient: Dolutegravir (as sodium)

Sponsor: ViiV Healthcare Pty Ltd

July 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the curve
$AUC_{0\text{-}24h}$	Area under the curve from time zero to 24 hours
$AUC_{0\text{-}\infty}$	Area under the curve from time zero extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the curve from time zero to last measurable concentration
C_0	Concentration at time zero (dosing)
C_{24h}	Concentration at 24 hours
C_{max}	Maximum concentration
C_{min}	Minimum concentration
DLP	Data lock point
EMA	European Medicines Agency (European Union)
FDA	Food and Drug Administration (United States of America)
GMP	Good Manufacturing Practices
PK	Pharmacokinetics
Pop PK	Population pharmacokinetics
RMP	Risk management plan
SmPC	Summary of Product Characteristic (European Union)
TGA	Therapeutic Goods Administration
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	Extension of indications, and new dose form
Product name:	Tivicay, and Tivicay PD
Active ingredient:	Dolutegravir (as sodium)
Decision:	Approved
Date of decision:	15 September 2021
Date of entry onto ARTG:	20 September 2021
ARTG numbers:	205212, 312781, 312782, and 340591
, *Black Triangle Scheme:*	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved
Sponsor's name and address:	ViiV Healthcare Pty Ltd Level 4, 436 Johnston Street Abbotsford, VIC 3067
Dose forms:	Tivicay: film-coated tablet Tivicay PD: dispersible tablet
Strengths:	Tivicay: 10 mg, 25 mg and 50 mg Tivicay PD: 5 mg
Container:	Bottle
Pack sizes:	Tivicay 10 mg, 25 mg and 50 mg: 30 tablets Tivicay PD 5 mg: 60 tablets
Approved therapeutic use:	*Tivicay and Tivicay PD are indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children of at least 4 weeks in age or older and weighing 3 kg or more (see Section 4.4 Special Warnings And Precautions For Use, Dual regimens).*
Route of administration:	Oral
Dosage:	Tivicay and Tivicay PD therapy should be initiated by a physician experienced in the management of HIV infection. Dolutegravir is available as film-coated tablets for patients aged at least 6 years and weighing at least 14 kg. Dolutegravir is also available as dispersible tablets for

	patients aged at least 4 weeks and weighing at least 3 kg, or for patients in whom film-coated tablets are not appropriate. The bioavailability of film-coated tablets and dispersible tablets is not comparable therefore they must not be used as direct replacements (see Section 5.2 Pharmacokinetic Properties, of the Product Information). For example, the recommended adult dose for film-coated tablets is 50 mg versus 30 mg for dispersible tablets. Patients changing between film-coated and dispersible tablets should follow the dosing recommendations that are specific for the formulation. Tivicay and Tivicay PD can be taken with or without food. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Product background

This AusPAR describes the submission by ViiV Healthcare Pty Ltd (the sponsor) to register Tivicay (dolutegravir) 10, 25 and 50 mg film-coated tablets (bottle); and Tivicay PD (dolutegravir) dispersible 5 mg tablets (bottle) for the following proposed extension of indications:

> *Tivicay and Tivicay PD are indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children of at least 4 weeks in age or older and weighing 3 kg or more over 6 years of age*

At the time of submission, dolutegravir had been approved for use in Australia for the indication below:

> *Tivicay is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 6 years of age (see Section 4.4 Special Warnings And Precautions For Use, Dual regimens).*

The sponsor proposed to modify this indication to include a new patient population by extending the usage of dolutegravir to include children aged less than 6 years old.

In addition, the sponsor proposed to register a new dose form and strength of the previously approved active substance dolutegravir in the form of Tivicay PD, a dispersible tablet containing 5 mg dolutegravir.

The sponsor also proposed to amend the existing dosing recommendations for children to align the dosing recommendations to the World Health Organization defined weight bands and to extend the 50 mg film-coated tablet to include children weighing ≥ 20 kg.

Treatment of HIV infection in children

The predominant mode of transmission of HIV infection in children in Australia is mother-to-child-transmission. The natural history of HIV infection in perinatally infected children is characterised by rapid disease progression in a significant proportion of neonates. Early treatment initiation is associated with immune, growth, and neurodevelopmental benefits. Rapid initiation of antiretroviral treatment is critical for infants and children aged < 1 year who carry the highest risk of rapid disease progression and mortality.[1]

In Australia, the number of new HIV diagnoses has remained < 10 per year in patients less than 14 years of age.[2]

Unique issues for HIV-infected children include the potential for perinatal transmission of viruses resistant to antiretroviral therapy regimens taken by mothers during pregnancy and breastfeeding; special consideration of adverse events as children take drugs during growth and development and will be required to take antiretroviral therapy for much longer than adults, and the need for age appropriate once daily formulations, preferably fixed dose (scored) dispersible combinations but which can be dosed flexibly in growing children, or may require different ratios of drugs from those used in adults.

Current treatment options

Combination antiviral therapy with HIV-1 protease and reverse transcriptase inhibitors has significantly reduced AIDS-related morbidity and mortality. However, emerging multi-class drug-resistant HIV strains and long-term toxicities warrant development of new classes of antiretroviral therapy. Integrase strand transfer inhibitors (INSTIs) are a newer class of antiretroviral drugs designed to block the action of the integrase viral enzyme, which catalyses two key steps in the HIV life cycle and is responsible for insertion of the viral genome into the DNA of the host cell. Since genome integration is a vital step in retroviral replication, it is an attractive target for HIV therapy.

Although there has been substantial improvement in antiretroviral therapy coverage over the last few years, only half of children have access to antiretroviral therapy. Rapid disease progression and high early mortality require that antiretroviral therapy is started early in life and many children still die before they are diagnosed. In both well-resourced and resource-limited settings, there is a need for alternative first and second line regimens which can be given in the face of possible transmitted resistance (from prevention of mother to child transmission) or resistance arising from first-line antiretroviral therapy, whether boosted protease inhibitor (bPI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based.

Standard antiretroviral therapy for children is a NNRTI or bPI, plus 2 nucleoside reverse transcriptase inhibitor (NRTIs) and, where possible, fixed dose combinations (dosed once a day) are preferred to support adherence. Not all approved drugs are approved for use in young children. The most frequently used fixed dose combination in adolescents is efavirenz + tenofovir disoproxil + emtricitabine; or lamivudine.

[1] Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PediatricGuidelines.pdf
[2] Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2021. Sydney: Kirby Institute, UNSW Sydney; 2021. Available at: https://data.kirby.unsw.edu.au/hiv

Clinical rationale

New treatment regimens need to be potent, durable, well-tolerated and available in acceptable once daily formulations with appropriate drug ratios. Ideally, regimens should be robust with a high barrier to resistance, have minimal cross-resistance, and minimal interactions with anti-TB drugs.

Dolutegravir (DTG) is an HIV-1 integrase strand transfer inhibitor (INSTI) which can be given once daily and has a documented long term safety profile, low pharmacokinetic variability, few drug interactions, rapid and robust virological response with an optimised background treatment, a known resistance profile and high potency at a low milligram dose. It therefore offers and attractive profile for children starting first line antiretroviral therapy and those switching to second line for reasons of toxicity or failure.

Doltegravir is already approved for adults and adolescents weighing ≥ 40 kg. Paediatric indications vary, for instance the indication in the European Union and Australia is for children weighing ≥ 15 kg while Tivicay (doltegravir) is approved in the United States of America and Switzerland for children ≥ 30 kg. These indications are based on previously submitted interim data from the P1093 trial (Study ING112578).

Data presented in this application supports the new proposed dosing recommendations based on observed exposures relative to exposures observed in adults at the approved doses.

The two trials submitted included both antiretroviral therapy-naïve and antiretroviral therapy-experienced children.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 January 2014 for the following indication:[3]

> *Tivicay is indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children over 12 years of age and weighing 40 kg or more.*

At the time the TGA considered this submission, similar submission had been approved in the European Union (EU), United States of America (USA) and Canada. A similar submission was under consideration in Switzerland

The following table summarises these submissions and provides the indications where approved.

[3] AusPAR for Tivicay dolutegravir Viiv Healthcare Pty Ltd PM-2012-04124-1-2, 19 May 2014
Available at: https://www.tga.gov.au/auspar/auspar-dolutegravir-sodium

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	11 December 2019	Approved on 11 January 2021	*Tivicay is indicated in a combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and paediatrics aged at least 4 weeks and weighing at least 3 kg (see Warnings and Precautions-Dual regimens).*
United States of America	12 December 2019	Approved on 12 June 2020	*Tivicay and Tivicay PD are indicated in combination with other antiretroviral agents f or the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults (treatment-naïve or -experienced) and in paediatric patients (treatment- naïve or -experienced but integrase strand transfer inhibitor [INSTI]-naïve) aged at least 4 weeks and weighing at least 3 kg.*
Canada	28 January 2020	Approved on 27 January 2021	*Tivicay, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults and in INSTI-naïve paediatric patients aged 4 weeks and older and weighing at least 3 kg.*
Switzerland	7 February 2020	Under evaluation	*Treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults, adolescents and children.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2020-03495-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2020
First round evaluation completed	26 March 2021
Sponsor provides responses on questions raised in first round evaluation	26 May 2021
Second round evaluation completed	26 May 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 July 2021
Sponsor's pre-Advisory Committee response	20 July 2021
Advisory Committee meeting	24 August 2021
Registration decision (Outcome)	15 September 2021
Completion of administrative activities and registration on the ARTG	21 September 2021
Number of working days from submission dossier acceptance to registration decision*	218

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

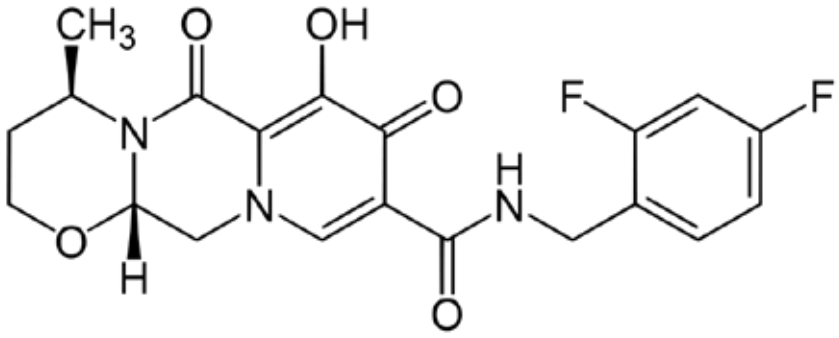
The following guidelines adopted by the TGA were relevant to this submission:

- EMEA/CPMP/EWP/633/02 Rev. 3 Guideline on the clinical development of medicinal products for the treatment of HIV infection. Effective 1 January 2017.
- Paediatric HIV Infection: Drug Product Development for Treatment. Guidance for Industry March 2019 United States Food and Drug Administration (US FDA).

Quality

Tivicay film-coated tablets and Tivicay dispersible tablets both contain dolutegravir (as sodium) as the active ingredient. The chemical structure is shown below in Figure 1: Dolutegravir chemical structure

Figure 1: Dolutegravir chemical structure



Tivicay 10, 25 and 50 mg film-coated tablets are currently supplied in Australia and were previously evaluated for quality at the time of initial registration of this drug.[3]

In this submission the sponsor proposes to register a new dose form and strength of the previously approved active substance dolutegravir in the form of Tivicay PD. Tivicay PD was developed to provide a dispersible tablet containing 5 mg of dolutegravir drug substance, equivalent to 5.26 mg as the sodium salt, with a small tablet size to minimise excipients dosed to children and aid swallowing if dosed directly to mouth. A sweetener and flavour were also included for palatability.

Tivicay film-coated tablets

Tivicay 10, 25 and 50 mg film-coated tablets each contain 10.5 mg, 26.3 mg or 52.6 mg of dolutegravir sodium, equivalent to 10 mg, 25 mg or 50 mg of dolutegravir free acid.

Tivicay 10 mg film-coated tablets are white, film-coated, round, biconvex tablets debossed with 'SV 572' on one side and '10' on the other side.

Tivicay 25 mg film-coated tablets are pale yellow, film-coated, round, biconvex tablets debossed with 'SV 572' on one side and '25' on the other side.

Tivicay 50 mg film-coated tablets are yellow, film-coated, round, biconvex tablets, debossed with 'SV 572' on one side and '50' on the other side.

Tivicay film-coated tablets contain mannitol as an excipient.

Tivicay film-coated tablets are supplied in HDPE (high density polyethylene) bottles containing 30 tablets. The tablet bottles contain a desiccant.

Tablets should be stored below 30°C in the original package in order to protect against moisture. Keep the bottle tightly closed when stored. The desiccant should not be removed.

Tablets have a shelf life of 36 months. The expiry date can be found on the packaging.

Tivicay PD dispersible tablets

Tivicay PD 5 mg dispersible tablets each contain 5 mg of dolutegravir (as dolutegravir sodium). Tivicay PD dispersible tablets each contain 5.26 mg of dolutegravir sodium, equivalent to 5 mg of dolutegravir free acid.

Tivicay PD 5 mg dispersibile tablets are white, round, biconvex tablets debossed with 'SV H7S' on one side and '5' on the other side.

Tivicay PD tablets contain mannitol and sucralose as excipients.

Tivicay PD dispersible tablets are supplied in HDPE (high density polyethylene) bottles containing 60 tablets. The bottles contain a desiccant. A dosing cup and syringe are supplied with the pack.

Tablets should be stored below 30°C in the original package in order to protect against moisture. Keep the bottle tightly closed when stored. The desiccant should not be removed.

Tablets have a shelf life of 36 months. The expiry date can be found on the packaging.

Conclusions and recommendations

Approval was recommended for registration of the proposed product from a pharmaceutical chemistry perspective.

Good Manufacturing Practice (GMP) clearance information for multiple sites of drug substance manufacture was in question and will either expire before a decision is expected or does not include scope for the manufacture of dolutegravir sodium. It is anticipated that the sponsor will be able to provide a response to the TGA that addresses these issues prior to a decision being made. The pharmaceutical chemistry evaluator requested that the sponsor liaise with the manufacturing quality branch to ensure GMP clearance information for these sites is valid.

Nonclinical

No new toxicological data were submitted in this application to support the extension of indications. The sponsor referred to previously submitted studies supporting the initial registration of dolutegravir.[3] The assessment for the current submission was based on studies reviewed in the previous nonclinical evaluation report prepared for submission PM-2018-05410-1-2.

No new major target organs of toxicity were identified in juvenile animals, and no significant toxicity was observed in offspring of rats dosed with dolutegravir during gestation and lactation. Overall, juvenile animals did not appear to be more prone to dolutegravir toxicity compared to adults.

There were no nonclinical objections to the proposed extension of indications to include children aged at least one month and weighing ≥ 3 kg and increase the dose for children weighing ≥ 14 kg.

No changes were required to the nonclinical sections of the product information.

The Delegate commented that the nonclinical sections of the product information will be updated with the pre-ACM response to include the approved text from submission PM-2020-00130-1-2.

Clinical

Summary of clinical studies

The clinical dossier consisted of the following:

- Five clinical pharmacology studies providing pharmacokinetic, pharmacodynamic and safety pharmacology data (Studies 200401, 205893, 201296, ING114556, and ING112578)
- One population pharmacokinetic analysis (Report 2019N424147-00)

- One pivotal efficacy/safety study (Study ING112578)
- Multiple literature references.

Pharmacology

Pharmacokinetics

The evaluator commented that this submission was essentially based on relative bioavailability data of the new formulation, the 5 mg dispersible tablet, compared to the approved 50 mg film-coated tablet.

Study 201296 (Odyssey trial, pharmacokinetics in target population)

This is an ongoing, open label, study that was planned to last 96 weeks. The clinical study report submitted contained available safety and pharmacokinetic (PK) data from two of the weight band PK sub-studies (called PK sub-studies) through to the cut-off date of 28 February 2019.

It was an open label, multicentre, randomised, non-inferiority, 96 week, 2-arm, study conducted in 8 countries (Uganda, Zimbabwe, South Africa, Thailand, UK, Portugal, Spain and Germany) from September 2016 to cut-off date of February 2019.

The PK sub-studies were added in Version 3.0 of the ODYSSEY trial protocol. The PK sub-studies enrolled a sub-population of ODYSSEY trial participants at clinical sites in Uganda, South Africa, and Zimbabwe.

The primary objective was to evaluate the efficacy and safety of once daily dolutegravir antiretroviral therapy compared with standard of care in children and adolescents starting first or second line antiretroviral therapy in resource limited and well-resourced settings.

The objectives of PK sub-studies (WB-PK1-WB-PK2) were:

- To provide PK data for children in the 3 World Health Organization weight bands < 14 kg (lower WB-PK1) ongoing
- To provide PK data with dolutegravir 25 mg (film-coated tablets) in children 14 to < 20 kg and 20 to < 25 kg (WB-PK1, part I, completed)
- To provide PK data with dolutegravir dosed at 25 mg (dispersible tablets) in children 14 to < 20 kg and 30 mg (dispersible tablets) or 50 mg (film-coated tablets) in children 20 to < 25 kg (WB-PK1, part II, completed)
- To provide PK data with dolutegravir 25 mg, 35 mg, and 50 mg film-coated tablets in a cross-over design in children 25 to <40 kg (WB-PK2, completed)
- To provide safety data for new dosing

Film coated tablets: The evaluator noted that:

> 'following administration of the 25 mg film-coated tablet dose in the 14 to < 30 kg weight range, geometric means for both the area under the concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) and mean concentration at 24 hours (C_{24h}) were below the PK targets agreed with the US FDA. The geometric mean $AUC_{0\text{-}24h}$ target was achieved following administration of a 35 mg film-coated tablet dose in the 30 to < 40 kg weight band, however, the geometric mean C_{24h} was lower. Geometric mean $AUC_{0\text{-}24}$ and C_{24} were comparable to the predefined target following 50 mg film-coated tablet administration at steady state in the 20 to < 40 kg weight band. Thus, the sponsor concluded that the 50 mg film-coated tablet was a suitable dose and format for participants weighing 20 to < 40 kg. The geometric mean trough concentrations (C_0) were comparable to C_{24h} at all doses tested following film coated tablet administration.'

The Delegate comment this is reflected in the proposed revised dosing in the PI for the film coated tablets.

Dispersible tablets: Following the administration of dispersible tablets in the weight bands spanning 6 to < 25 kg, steady state geometric mean $AUC_{0\text{-}24h}$ and C_{24h} were comparable to predefined targets except in the 6 to < 10 kg weight band where following a 15 mg dispersible tablet dose, the geometric mean C_{24h} was lower but the data was highly variable (coefficient of variation 396%). The steady state geometric mean $AUC_{0\text{-}24h}$ was > 45% higher following dispersible tablet administration compared to film-coated tablet administration in the weight bands spanning 10 to < 25 kg. Following administration of dispersible tablet at doses tested, geometric mean C_0 concentrations were comparable to C_{24h}.

Evaluator conclusions: The PK sub-studies were not designed for dose-finding, but instead for evaluating specific dolutegravir doses and formulations administered according to WHO weight bands and anticipated to provide simplified and efficacious dosing schedules.

Plasma dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} values associated with efficacy in adults were used as PK targets for the paediatric population. A range of expected values were established to account for the inherent variability in observed exposures in infants and children. The primary PK endpoint was C_{24h}, with $AUC_{0\text{-}24h}$ as a secondary endpoint. No targets were selected for maximum concentration (C_{max}).

There was consistency between doses and formulations in terms of their PK outcomes, allowing for the bioavailability difference between film-coated tablets and dispersible tablets:

- There was greater variance in the C_{24h} values relative to $AUC_{0\text{-}24h}$ or C_{max}.
- With the relatively low numbers per weight band, this variance could lead to chance outcomes not reflective of the larger population and not consistent with the bulk of the study data. This may be the cause for the lower than expected geometric mean C_{24h} observed.

Study 205893 (Relative bioavailability)

This study was conducted in adult subjects, in two parts:

- *Part 1* was a randomised, open label, 2 period, 2 sequence, crossover study in 14 adult subjects to evaluate the bioavailability of two strengths of the film-coated tablets, the 10 mg dolutegravir tablet compared with the 50 mg dolutegravir tablet under fasted conditions

  The study found that following single oral administration under fasted conditions 50 mg given as 5 x 10 mg tablets was equivalent to 50 mg given as 1 x 50 mg with respect to C_{max}, area under the curve from time zero to last measurable concentration ($AUC_{0\text{-}t}$) and area under the curve from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$).

- *Part 2* was a randomised, open label, 3 period, 6 sequence, crossover study in 24 adult subjects to evaluate the bioavailability of 5 mg dolutegravir dispersible tablets compared to 25 mg dolutegravir film-coated tablets administered under fasting conditions.

  Following oral administration under fasted conditions of 5 mg dolutegravir dispersible tablets (5 tablets) delivered higher plasma dolutegravir C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ compared with 25 mg dolutegravir (one film-coated tablet). The results were similar for the dispersible tablets administered as a dispersion or directly into the mouth.

The relative bioavailability of the dispersible tablet is approximately 1.6x higher than the film coated tablet.

The effect of food on the bioavailability of the dolutegravir dispersible tablets has not been evaluated.

Studies 200401 and ING114556

These studies include bioavailability of the dolutegravir granules versus dispersible tablets and film coated tablets. Registration of the dolutegravir granules has not been requested.

Study ING112578

The primary objectives of the study were to select a dolutegravir dose that achieved similar exposure to the adult dose for integrase strand transfer inhibitor (INSTI)-naïve participants of 50 mg film-coated tablets once daily.

The study met the primary objective of achieving similar plasma dolutegravir exposures for the dispersible tablet to the 50 mg film coated tablet.

The evaluator concluded that the use of weight bands rather than age ranges was best demonstrated by the 6 to < 10 kg enrolment weight band which was distributed across 2 age cohorts (≥ 4 weeks to < 6 months; and ≥ 6 months to < 2 years). Participants < 6 months of age demonstrated adequate exposures when receiving a dose of dolutegravir dispersible tablets 10 mg once daily but participants ≥ 6 months of age receiving dolutegravir dispersible tablets 10 mg once daily showed relatively lower C_{24h} concentrations compared to those < 6 months of age. A dose of dolutegravir dispersible tablets 15 mg once daily was more appropriate and achieved better results (comparable to participants < 6 months).

The Delegate commented the proposed PI includes dosing stratified by age (< 6 months; ≥ 6 months) for the 6 to < 10 kg weight band. This has also been adopted by the European Medicines Agency and Health Canada, while the US FDA recommends a dispersible tablet dose of 15mg for all patients weighing 6 to < 10kg, regardless of age (as per FDA Prescribing information, Tivicay, Tivicay PD, revised March 2021).

Population pharmacokinetic data

Report 2019N424147_00

The application was reviewed by the TGA's population pharmacokinetics (PopPK) evaluator and is summarised below:

The sponsor submitted a PopPK and graphical PK-safety analysis report (Report 2019N424147_00) in support of the proposed changes. The model was previously submitted as part of the another submission (PM-2018-05410-1-2; extension of indications (indicated aged) to include 6 years of age and above) and considered by the Pharmacometrics Working Group along with the European Medicines Agency evaluation reports at the time. The Pharmacometrics Working Group noted that the then proposed dosing would lead to trough concentrations below 0.5 µg/mL (proposed target) in nearly up to 25% simulated subjects in the 15 < 20 kg and 20 < 30 kg weight groups.

The proposed increase in dosing for the 15 kg to 40 kg weight group reflects this observation made in the previous submission.

The objectives of the current analysis were to evaluate the predictive performance of a previously-developed model, update the model with additional data in order to characterise the PK of dolutegravir, identify and quantify covariates that explain variability, and support dolutegravir dosing recommendations for the paediatric population. In addition, *post-hoc* plasma dolutegravir exposure metrics were derived for use in exposure-response analyses for safety and efficacy.

Conclusions: The PopPK model provided a good description of the overall data with a stable model. Considering prediction-corrected visual predictive checks, the predictive performance of the PopPK model appeared to be satisfactory. The simulations in general support the proposed paediatrics dosing and the proposed increase in dosing for the 15 kg

to 40 kg weight group. The amended proposed dosing in this age group whilst improving the C_{24h} concentrations (to be in line with adult values) would result in an increased Cmax in relation to that observed in the adult population, but still within the range of highest studied dose. In the exploratory analysis, there was a lack of exposure-safety relationship.

Consideration could be given to adding a twice daily dosing option for children in the PI, which would reduce the C_{max} whilst increasing the C_{min}, at the expense of convenience and adherence issues, as done by the European Medicines Agency. If this is requested, a summary table with exposure parameters and dosing table for the twice daily dosing would be required in the PI in PK section (similar to Table 12 in the current PI) and dosing table (similar to Table 1b in section 4.2 of the PI).

Given the limitations with establishing the food effect on the dispersible tablet formulation, the PK section in the PI should reflect the lack of study describing the effect of food on the dispersible tablet formulation.

Sponsor's response to the second round population pharmacokinetics report (14 May 2021)

The sponsor acknowledged the Pop PK evaluator's comments regarding increased C_{max} values across the proposed paediatric weight bands and reiterated that there was no exposure response relationship between any dolutegravir concentration and the probability of adverse clinical or laboratory events.

While a twice daily dosing approach would result in lower C_{max} values across the weight bands, the sponsor expressed concerns regarding medication adherence in paediatric patients and the potential for medication errors. It was also stated that the doses cannot be equally divided without changing the total daily dose for some weight bands. (Response to the TGA, Tivicay (dolutegravir 5 mg) Dispersible Tablet). There could be confusion between this potential use of splitting the dose and situations where twice daily dosing is required, for example: in the presence of a strong enzyme inducer.

Delegate's comments

The response from the sponsor is acknowledged, however the twice daily dosing option in the European Union (EU) PI warrants discussion, given the PopPK evaluator comments. The EU Summary of Product Characteristics (SmPC) includes a twice daily dosing option in children for both the film coated tablets and dispersible tablets which may give clinicians an alternative for patients where there are tolerability issues with once daily dosing.

The PopPK evaluator also noted the limitations with establishing the food effect on the dispersible tablet formulation and advised that the PK section in the PI should reflect the lack of information describing the effect of food on the dispersible tablet formulation.

The sponsor acknowledged the evaluator's comments about the lack of data characterising the specific impact of food on dolutegravir dispersible tablet formulation and proposed a statement in the PI accordingly, consistent with the wording in the approved EU SmPC. This has not yet been included in the PI provided in response to the clinical dossier reports and was brought to the attention of the Sponsor. The Sponsor has confirmed that the text on food effect as proposed in response to the PopPK report will be included in the updated PI as part of the pre-Advisory Committee on Medicines (ACM) response (as per sponsor email, 4 June 2021).

Pharmacodynamics

Exposure response and exposure safety analyses were conducted as part of Studies ING 112578 and 201296 and the PopPK Report 2019n424147. None of the dolutegravir exposure metrics (C_{24h}, $AUC_{0\text{-}24h}$, and C_{avg}) were predictive of virologic response over the range of exposures in this analysis and are most likely maintaining a near maximum drug effect.

Based on linear regression analysis of data collected on PK visits, there were no apparent relationships between plasma dolutegravir C_{max} or AUC_{0-24h} and clinical laboratory data, as raw values or as change from Baseline or to any of the adverse events of special interest.

Efficacy

Study ING112578

Note: this is also known as Study P1093.

This was a Phase I/II, multi-centre, open-label, non-comparative, pharmacokinetic, safety, tolerability and antiviral activity of dolutegravir (GSK1349572), a novel integrase inhibitor, in combination regimens in HIV-1 infected infants, children and adolescents: Cohorts I to V, Interim Report**.**

This was an open label multicentre, non-comparative study conducted at 34 sites in 9 countries from April 2011 to a cut-off date of 30 April 2019.

The evaluator commented that Study ING112578 was an ongoing efficacy study but the interim report included in this submission related to the PK results. The primary aim of this study was to select a dolutegravir dose that achieved similar exposure to the previously submitted and approved adult dose for integrase strand transfer inhibitor (INSTI)-naïve participants of 50 mg film-coated tablets once daily. The efficacy data was a secondary outcome of the study.

Participants were enrolled into two sequential stages for each of five age defined cohorts which later included weight bands.

- *Stage 1* Participants underwent intensive PK sampling for 5 days and were monitored for safety and tolerability of dolutegravir. Once the dose was accepted, Stage 1 was ceased.
- *Stage 2* Participants were treated for 48 weeks and evaluated for PK parameters, safety and tolerability.

After Week 48, all participants transitioned to long term follow up and could remain on the study for approximately 3 additional years (144 additional weeks of follow up, for a total of 192 weeks on study).

Primary objectives:

- To select a dose for each formulation of dolutegravir for chronic dosing in infants, children and adolescents that achieves similar exposure to the dolutegravir 50 mg once daily adult dose.
- To determine the safety and tolerability of dolutegravir in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.
- To evaluate the steady-state PK of dolutegravir in combination with an optimised background therapy in treatment experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of dolutegravir.

Secondary objectives:

- To evaluate the antiviral activity of dolutegravir in combination with an optimised background therapy by measuring virologic response in infants, children and adolescents at 24 and 48 weeks
- To evaluate the effect on immunologic response from Baseline to 24 and 48 weeks
- To assess changes in HIV-1 genotype and phenotype to dolutegravir and other components of the optimised background therapy in participants experiencing virologic failure

- To determine dolutegravir exposure, its variability and clinical covariates that impact dolutegravir disposition (for example: age, weight) using intensive and sparse sampling and PopPK analysis
- To determine the extended long term (≥ 48 weeks) safety, tolerability and efficacy of dolutegravir in HIV-1 infected infants, children and adolescents
- To explore the relationship between dolutegravir exposure and the antiviral activity
- To evaluate PK, safety and tolerability profile of dolutegravir when dosed by weight bands.

Results

The primary objective of the interim report was the pharmacokinetic outcome and dose finding.

The clinical study report presented efficacy data for participants who completed a minimum of the Week 24 study visit and focused on those participants who received the proposed dose (that is, the proposed dose efficacy population).

Table 3: Study ING112578 Antiviral and immunological activity through Week 24 and Week 48 (Proposed dose efficacy population)

	Week 24 N = 58		**Week 48 N = 24**	
	n/N	**% (95% CI)**	**n/N**	**% (95% CI)**
Proportion of participants with HIV RNA < 50 copies/mL[a]	36/58	62.1 (48.4 - 74.5)	16/24	66.7 (44.7 – 84.4)
Proportion of participants with HIV RNA < 400 copiess/mL	50/58	86.2 (74.6 - 93.9)	18/24	75 (53.3 – 90.2)
	Median (n*)	**(Q1, Q3)**	**Median (n*)**	**(Q1, Q3)**
Change from Baseline in CD4+ cell count (cells/mm)	105 (57)	(-93, 338)	149 (23)	(-17, 291)
Change from Baseline in CD4+ percent	5.1 (57)	(1, 9.3)	8 (23)	(0, 11)

N = Number of participants in each cohort;

n* = Number of participants contributing data

For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of participants.

For continuous endpoints: median changes with the first and third quartiles were reported. Normal distributions were assumed for continuous endpoints.

Snapshot algorithm was used in the RNA analyses.

Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the Protocol Team, and discontinuation for non-treatment related reasons with the last HIV RNA ≥ 400/50/LLQ copies/mL.

a Results of < 200 copies/mL from HIV-1 RNA testing using a lower limit of determination of 200 copies/mL were censored to > 50 copies/mL in this analysis

Table 4: Study ING112578 Outcomes based on plasma HIV-1 RNA < 50 copies/mL (Proposed dose efficacy population; snapshot analysis)

	Week 24 N=58 n (%)	Week 48 N=24 n (%)
Virologic Success[a]	36 (62.1)	16 (66.7)
Virological Failure[b]	22 (37.9)	8 (33.3)
Data in window not below threshold	22 (37.9)	6 (25)
Discontinued while not below threshold	0	2 (8.3)
No Virologic Data	0	0

Note: n (%) = Number (percent) of participants in each subcategory.

Note: Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 copies/mL were censored to > 50 copies/mL in this analysis.

a. Virologic success was defined as plasma HIV-1 RNA < 50 copies/mL; Snapshot algorithm was used in HIV-1 RNA analysis

b. Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the protocol team, and discontinuation for non-treatment related reasons with the last HIV RNA ≥ 50 copies/mL.

The antiviral efficacy at < 400 copies/mL through Week 24 and Week 48 and < 50 copies/mL through Week 48 was comparable to that observed in a similar treatment-experienced adult study of dolutegravir (Study ING111762, SAILING trial).

Table 5: Study ING112578 Antiviral response in Study ING112578 compared to that of adult data from Study ING111762 (Sailing trial) (Snapshot analysis)

	P1093[a] PD Efficacy Population (N=58)	SAILING[b] Per Protocol Population (N=354)
Week 24	n/N (%)	n/N (%)
Proportion of participants with HIV RNA < 50 copies/mL	36/58 (62)	281/354 (79)
Proportion of participants with HIV RNA < 400 copies/mL	50/58 (86)	307/354 (87)
Week 48	n/N (%)	n/N (%)
Proportion of participants with HIV RNA < 50 copies/mL	16/24 (67)	251/354 (71)
Proportion of participants with HIV RNA < 400 copies/mL	18/24 (75)	278/354 (79)

P1093 = Study ING112578, SAILING = Study ING111762 (submitted in initial application)

Note: n/N=number of responders/number of participants

a Proposed dose efficacy population from Study P1093 (Table 61)

b *Cahn, 2013* and public results database for NCT01231516, 2019

Efficacy was a secondary objective of this ongoing study, which is planned for 96 weeks of treatment. Complete results were available for 24 weeks and incomplete data for 48 weeks.

Participants with results through Week 48 came exclusively from the ≥ 35 kg weight band recruited into Cohort I and IIA and receiving the 50 mg film-coated tablets, due to the sequential enrolment strategy of the study.

Favourable antiviral activity (< 400 copies/mL and < 50 copies/mL) was demonstrated through Week 24 in the proposed dose efficacy population for participants taking dolutegravir with optimised background therapy). Immunologic benefit was also observed when considering change from Baseline in CD4+ cell count and CD4+ percent.

Sustained antiviral activity and immunological benefit was maintained through Week 48 in the proposed dose efficacy population (N = 24).

Through to the interim data cut-off of 14 February 2019, 36/142 (25%) participants met protocol defined virologic failure criteria (had confirmed plasma HIV-1 RNA > 400 copies/mL).

Table 6: Study ING112578: Protocol defined virologic failure over time

	Through Week 24 N=142 n (%)	Post Week 24 Through Week 48 N=142 n (%)	Post Week 48 N=142 n (%)	Total N=142 n (%)
PDVF	20 (14)	8 (6)	8 (6)	36 (25)

PDVF = protocol defined virologic failure

The results were similar to that seen in similarly designed adult studies when using a 400 copies/mL threshold previously evaluated and approved. A slightly lower efficacy was seen in the paediatric study compared to the adult study at 24 weeks using the 50 copies/mL threshold.

The evaluator concluded that the numbers in this single non-comparative study were small, but provided acceptable antiviral activity and immunologic benefit through to 48 weeks.

The Delegated commented that the sponsor is requested to provide the completed study report for Study ING112578 as a future submission, when available.

Safety

The safety database provided was limited especially for children < 6 years. The data presented were from the ongoing efficacy Study ING 112578 (Study P1093) and the PK subset of Study 201296 (ODYSSEY trial), in addition to post-marketing data.

Cough, pyrexia, diarrhoea, rhinorrhoea, vomiting, and nasal congestion were the most common adverse events reported, consistent with common childhood infections. No new safety information was identified, with the exception of a case of anaphylactic reaction in a single patient.

Risk management plan

The sponsor has applied to extend the indications of Tivicay (dolutegravir) is currently approved for the treatment, in combination with other antivirals, of HIV in adults and children over 6 years of age with daily oral dosage of film coated tablets determined by age and body weight. The current submission seeks to extend the indications to include children under 6 years of age, and to register a new 5 mg dispersible tablet strength and dosage form to provide an appropriate formulation for infants. At the second round, the sponsor has changed the name of the dispersible formulation to Tivicay PD.

The most recently evaluated EU-risk management plan (RMP) was version 15.0 (date 15 January 2019; data lock point (DLP) 16 July 2018) and Australian specific annex (ASA) version 6 (date 12 March 2019). In support of the extended indications, and new tablet strength and dosage form, the sponsor has submitted EU-RMP version 16.0 (no date; DLP 30 April 2019) and ASA version 7 (date 22 June 2020). At the second round, the sponsor submitted EU-RMP version 16.2 (date 9 November 2020; DLP 30 April 2019) and annotated ASA version 7.1. The sponsor subsequently provided clean ASA version 7.1 during the second round evaluation upon request by the evaluator.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7: Summary of safety concerns. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity reactions	ü	–	ü	–
	Hepatobiliary disorders	ü	–	ü	–
	Depression (including suicidal ideation and behaviours, particularly in patients with a pre-existing history of depression or psychiatric illness)	ü*	–	ü	–
Important potential risks	Serious rash (DAIDS Grade 3 or 4)	ü	–	ü	–
	Neural tube defects	ü*	ü†‡	ü	–
Missing information	Use in elderly	ü	–	ü	–
	Use in pregnancy/breastfeeding	ü	ü†‡	ü	–
	Long term safety data	ü	ü‡	–	–

*Specific adverse reaction follow-up questionnaires

† Antiretroviral Pregnancy Registry (APR)

‡ Safety studies

The adequacy of the pharmacovigilance plan has been assessed at the second round of evaluation. The sponsor has provided as updated ASA which describes routine and additional pharmacovigilance activities. Routine pharmacovigilance has been proposed for all safety concerns. Additional pharmacovigilance has been proposed for the missing information 'use in pregnancy/breastfeeding' and 'long term safety data'. The pharmacovigilance plan is acceptable.

Routine risk minimisation activities are proposed for all safety concerns apart from the missing information relating to long term safety. At the second round the dispersible formulation has been renamed Tivicay PD, and the Consumer Medicines Information (CMI) has been revised to reduce the risk of medication error associated with lack of interchangeability of the dispersible formulation with the film coated tablets. The sponsor does not agree to include the CMI in the product packaging. This outstanding recommendation is referred to the delegate. The risk minimisation plan will be considered acceptable when the sponsor has committed to providing the CMI, which includes the instructions for use, in the product packaging.

The RMP evaluator had the following advice is for the Delegate:

- The sponsor has not updated the ASA to include healthcare professional (HCP) education to reduce the risk of interchangeability errors between formulations, but has actioned other recommended measures:
  - The trade name for the dispersible dose form has been renamed 'Tivicay PD' to distinguish it from the film coated 'Tivicay' tablets
  - The Tivicay PD CMI includes very clear warnings that Tivicay is not interchangeable with Tivicay PD
  - The sponsor commits to including the corresponding statements regarding non interchangeability to the CMI for Tivicay film-coated tablets prior to the market launch of Tivicay PD
  - The sponsor proposes to include corresponding wording on the product packaging.
- The sponsor's proposal is acceptable, as it is considered that the measures agreed to by the sponsor will be very visible and hence effective at achieving the desired goal of educating patients and HCPs that Tivicay and Tivicay PD formulations are not interchangeable. The product packaging has not been provided for review as the sponsor advised in the sponsor's response to TGA questions that it would be, however the sponsor's commitment to updating the product packaging is noted. The delegate is advised that the sponsor has agreed to this change and that the product packaging should include this warning. The delegate's attention is also drawn to the sponsor's commitment to update the CMI for Tivicay film-coated tablets prior to market launch of Tivicay PD.

The following advice is for the sponsor:

- The summary page of the Tivicay PD CMI has been updated with the Black triangle Scheme wording and symbol as requested, however the first page of the full CMI does not include the black triangle statement and symbol. The sponsor is referred the CMI template . The sponsor is reminded that the first page of the full CMI should be updated to include the black triangle statement and symbol as described in the CMI template.

  This issue should not impede registration for this product.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Tivicay and Tivicay PD EU-Risk Management Plan (RMP) (version 16.2, dated 9 November 2020, data lock point 30 April 2019), with Australian Specific Annex (version 7.1, dated March 2021), included with submission PM-2020-03495-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
>
> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As the indications for Tivicay are being extended into a significantly different population and there is now a distinct product Tivicay PD proposed for use in the paediatric population, Tivicay PD should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Tivicay PD (dolutegravir) is to be included in the Black Triangle Scheme. The consolidated PI for Tivicay and Tivicay PD and CMI for Tivicay PD must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

Recommendations to the Delegate

Following the second round RMP evaluation, there were two outstanding recommendations which were referred to the Delegate for consideration:

- Recommendation 1: The sponsor does not agree to amend the important identified risk of 'hypersensitivity' to read 'hypersensitivity, including anaphylaxis as recommended by the clinical evaluator. As justification, the sponsor provided further information on the single reported case that prompted the clinical evaluator's request. From an RMP perspective the risk of hypersensitivity was adequately covered with the current wording and it was preferable to keep the wording for the safety concern consistent with the EU-RMP. The sponsor commits to reporting on hypersensitivity reactions, including anaphylaxis if it occurs, in PSURs as a routine pharmacovigilance activity.
- Recommendation 2: The sponsor does not agree to include the CMI in the product packaging. For the purpose of risk minimisation it is expected that where a product requires reconstitution by consumers, as is the case with Tivicay PD, that the instructions for reconstitution will be included in the product packaging. This is necessary as the product cannot be used without these instructions. The reconstitution instructions for TIVICAY are included in the CMI, therefore the CMI should be included as a package insert in the product packaging. The sponsor's risk minimisation plan is not considered acceptable as currently proposed.

Delegates conclusions

The sponsor responded with concerns regarding including the CMI in the product packaging on 28 May 2021, including outdated requirements for hard copy prescribing information documents to be supplied with relevant products, updates to the CMI not being as readily incorporated into paper documents and supply of Tivicay/Tivicay PD being limited to major children's hospitals in Australia.

The TGA acknowledges the concerns expressed by the sponsor in their written response but notes that the dispensing pharmacist or prescriber may not always provide the CMI to the patient. It cannot be assumed that Tivicay/Tivicay PD will frequently be administered by parents/carers that are likely to have a higher than usual level of health literacy when it comes to caring for their children.

The Delegate also sought advice from the pharmaceutical chemistry evaluator regarding this matter. As per section 8(l) of TGO 91, it is a requirement for this drug product to include instructions for use either on the label or with a package insert. Currently, the carton label refers to the CMI. If the instructions for use were provided as a separate document, then that would be acceptable from a pharmaceutical chemistry perspective, but would require a slight revision to the carton labels to refer to this document instead.

Instructions for reconstitution for the dispersible tablets need to be included in the product packaging. The inclusion of instructions for use as a separate document in the packaging rather than the entire CMI would be considered acceptable.

The sponsor is requested to provide a formal response and indicate whether they intend to provide the instructions for use or CMI in the product packaging.

RMP evaluator recommendations regarding conditions of registration

The suggested wording for conditions of registration is as follows:

> *The Tivicay and Tivicay PD EU-Risk Management Plan (RMP) (version 16.2, dated 9 November 2020, data lock point 30 April 2019), with Australian Specific Annex (version 7.1, dated March 2021), included with submission PM-2020-03495-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*

As the indications for Tivicay are being extended into a significantly different population and there is now a distinct product Tivicay PD proposed for use in the paediatric population, Tivicay PD should be included in the Black Triangle Scheme as a condition of registration.

Risk-benefit analysis

Delegate's considerations

The submitted data are sufficient to recommend registration of the proposed changes, including extension of indication, updated changes to dosing recommendations and the new dispersible tablet formulation.

The main concern relates to the lack of interchangeability between the dispersible tablet and the film coated tablets and potential for confusion and medication error. This has been addressed by the sponsor in response to recommendations from the RMP evaluator and reflected in the revised PI and CMI.

The Delegate acknowledges that the twice daily dosing option for the dispersible tablet may lead to more confusion and error, given the differing total daily dose for once daily versus twice daily dosing in some weight bands. The Sponsor states that no specific safety issues have been observed to date with higher C_{max} and once daily dosing in children. Comment from the Advisory Committee on Medicines is sought as to whether this twice daily dosing option is needed and would afford more flexibility for younger patients with HIV infection in Australia.

Inclusion of instructions for use in the product packaging for the dispersible tablets is an outstanding issue to be addressed by the sponsor.

Proposed action

While a decision is yet to be made, at this stage the Delegate inclined to approve the registration of the product.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please provide the completed study report for Study ING112578 as a future submission, when available.***

The sponsor commits to provide the completed study report for Study ING112578 to the TGA when it becomes available.

2. ***Please also submit the completed study report, including long term safety and efficacy to 96 weeks, for Study 201296 (ODYSSEY) when available.***

The sponsor commits to provide the completed study report for Study 201296 (ODYSSEY trial) to the TGA when it becomes available.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Please comment on the option of including twice daily dosing for infants and children in the Product Information (PI), in the context of paediatric HIV therapy in Australia.***

   While the sponsor's concerns, including the potential for medication error, are acknowledged, a twice daily dosing option in infants and children for both the film coated tablets and dispersible tablets would provide an alternative for patients where there are tolerability issues with once daily dosing.

   The European Medicines Agency (EMA) has approved a twice daily dosing option for children, while the US Food and Drug Administration (FDA) and Health Canada have approved a once daily dosing schedule. The dosing proposed for Australia in children only includes the once daily dosing schedule.

   For infants and children weighing 6 to less than 10 kg, dosing for the dispersible tablet is consistent with the approved PI for Health Canada and the EMA where the dosing is stratified by age (< 6 months and ≥ 6 months).

   The US FDA have simplified the dosing for the 6 to less than 10 kg weight band, with the same dose regardless of age.

The ACM noted that the European PI comments on the possibility of twice daily dosing (that is, to split the total daily dose) for ease of administration in young children. Conversely, the Australian PI recommends doubling the dose with twice daily dosing in specific instances where there are concerns of sub-optimal drug concentrations, for example, to counterbalance the effect of drug-drug interactions. The ACM advised that splitting the dose to allow twice daily dosing would have marginal benefit on a very small group of children in the Australian cohort (those weighing between 3 kg and 20 kg, and less than 6 years of age). Given that these patients are managed by highly specialised physicians, the ACM were of the view that it is not critical to include this information in the PI. It is expected that treating physicians would be aware of the possibility for split dosing if required on a case by case basis.

The ACM noted that some weight ranges may require difficult divisions of dispersible tablets for divided doses, and to consider that the volumes of 5 mL to 10 mL of diluent required per dose may be a barrier to adherence for young children, particularly as this would be a long-term medication.

The ACM noted that the TGA risk management plan (RMP) evaluation area had initially recommended the entire CMI including administration instructions be available with each dispensing of the product, however, have since agreed that the instructions for use are sufficient. While the ACM were of the opinion that the dose administration instructions are very clear for the patient/carer, and should be included as a minimum with the existing packaging for Tivicay, their strong preference is for the CMI to be included as well.
The ACM also highlighted that the bioavailability of the two dosage forms (film coated tablet versus dispersible tablet) are not equivalent and discussed the possibility of medication dispensing errors. The ACM discussed the possibility of having a different shape or colour for the dispersible tablets to more clearly differentiate them from the film coated tablets. The pharmaceutical chemistry evaluator will need to be consulted for further comment; however, it was acknowledged there may be manufacturing limitations considering the product is already marketed worldwide.

The ACM noted that mitigation strategies had been put in place (such as labelling changes) to minimise dispensing errors and were supportive of these strategies.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Tivicay and Tivicay PD are indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children of at least 4 weeks in age or older and weighing 3 kg or more (see Section 4.4 Special Warnings And Precautions For Use, Dual regimens).*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Tivicay dolutegravir (as sodium) 10 mg, 25 mg, and 50 mg film-coated tablets (bottle) and Tivicay PD dolutegravir (as sodium) 5 mg dispersible tablets (bottle) indicated for the following extension of indications:

> *Tivicay and Tivicay PD are indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children of at least 4 weeks in age or older and weighing 3 kg or more (see Section 4.4 Special Warnings And Precautions For Use, Dual regimens).*

As such, the full indications at this time were:

> *Tivicay and Tivicay PD are indicated for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral agents in adults and children of at least 4 weeks in age or older and weighing 3 kg or more (see Section 4.4 Special Warnings And Precautions For Use, Dual regimens).*

The above extension of indications are inclusive of the previous approved indications.

Specific conditions of registration applying to these goods

- Tivicay PD (dolutegravir) is to be included in the Black Triangle Scheme. The consolidated PI for Tivicay and Tivicay PD and CMI for Tivicay PD must include the

black triangle symbol and mandatory accompanying text for five years, which starts from the date that the new indication is registered.

- The Tivicay and Tivicay PD EU-Risk Management Plan (RMP) (version 16.2, dated 9 November 2020, data lock point 30 April 2019), with Australian Specific Annex (version 7.1, dated March 2021), included with submission PM-2020-03495-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Tivicay and Tivicay PD approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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