Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Dolutegravir/Lamivudine

Proprietary Product Name: Dovato

Sponsor: ViiV Healthcare Pty Ltd

November 2019

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 medicines and medical devices.
- 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 (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An 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.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
3TC	Lamivudine
ABC	Abacavir sulfate
ABC/3TC	Abacavir/lamivudine
ACM	Advisory Committee on Medicines
AE	Adverse event(s)
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARTG	Australian Register of Therapeutic Goods
ARV	Anti-retroviral
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the plasma concentration time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration time curve from time zero to the last quantifiable time point
BE	Bioequivalence
c/mL	Copies per milliliter
CD4+	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention (USA)
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CK	Creatinine kinase
C_{max}	Maximum observed concentration
CMI	Consumer Medicines Information
CNS	Central nervous system

Abbreviation	Meaning
CSR	Clinical study report
CVW	Confirmed virologic withdrawal
DAIDS	Division of acquired immune deficiency syndrome
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
DTG + 3TC	Dolutegravir (50 mg single entity tablet) and lamivudine (300 mg single entity tablet)
DTG/3TC FDC	Dolutegravir (50 mg) and lamivudine (300 mg) fixed dose combination tablet
EMA	European Medicines Agency (EU)
EU	European Union
EU-RMP	European Union-Risk management plan
FDA	Food and Drug Administration (USA)
FDC	Fixed dose combination
FTC	Emtricitabine
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLS	Geometric least square
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice(s)
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
INSTI	Integrase strand transfer inhibitor
IRIS	Immune reconstitution inflammatory syndrome

Abbreviation	Meaning
ITT	Intent to treat
ITT-E	Intent to treat exposed
LDL	Low density lipoprotein
MATE1	Multidrug and toxin extrusion protein 1
MATE-2K	Multidrug and toxin extrusion protein 2K
mg	Milligram
mg/dL	Milligram per decilitre
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OCT2	Organic cation transporter 2
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PI	Product Information
PIP	Paediatric Investigation Plan (EU)
PK	Pharmacokinetic(s)
PP	Per Protocol
PSUR	Periodic safety update report
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SE	Single entity
SOC	System Organ Class
$t_{1/2}$	Elimination half-life
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir disoproxil fumarate (300 mg) and emtricitabine

Abbreviation	Meaning
	(200 mg) fixed dose combination tablet
ULN	Upper limit of normal
USA	United States of America
ZDV	Zidovudine
ZDV/3TC	Zidovudine/lamivudine

I. Introduction to product submission

Submission details

Type of submission:	New combination of previously approved active ingredients
Decision:	Approved
Date of decision:	11 September 2019
Date of entry onto ARTG:	16 September 2019
ARTG number:	309378
, *Black Triangle Scheme*	No
Active ingredients:	Dolutegravir (as sodium)/lamivudine
Product name:	Dovato
Sponsor's name and address:	ViiV Healthcare Pty Ltd PO Box 18095 Melbourne City, VIC, 8001
Dose form:	Tablet, film coated
Strength:	Dolutegravir (as sodium) 50 mg/lamivudine 300 mg fixed dose combination
Container:	Bottle
Pack size:	30
Approved therapeutic use:	*Dovato (a fixed-dose combination of dolutegravir and lamivudine) is indicated for the treatment of Human Immunodeficiency Virus-1 (HIV-1) infection in antiretroviral treatment-naïve adults and adolescents (from 12 years of age weighing at least 40 kg) who have no known or suspected resistance to either antiretroviral component (see section 5.1 Pharmacodynamic Properties, Clinical trials).*
Route of administration:	Oral
Dosage:	*Adults and Adolescents* The recommended dose of Dovato in adults and adolescents weighing at least 40 kg is one tablet (containing 50 mg of dolutegravir and 300 mg of lamivudine) once daily. For further information refer to the Product Information (PI).

Product background

This AusPAR describes the application by ViiV Healthcare Pty Ltd (the sponsor) to register Dovato (dolutegravir (as sodium)/lamivudine) fixed dose combination tablet for the following proposed indication:

> *Dovato (dolutegravir/lamivudine) is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age weighing at least 40 kg, who have no known or suspected resistance to either antiretroviral component.*

Human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS). HIV damages the immune system and without treatment can lead to serious infections and cancers over time. The late stage of HIV infections is called AIDS. There are 2 main types of this virus: type 1 (HIV-1) and type 2 (HIV-2). HIV-1 is the most common type of HIV and occurs all over the world and around 95% of people living with HIV have HIV-1. HIV-2 is mainly present in West Africa, but is slowly starting to appear in other regions including the United States of America (USA), Europe and India. According to the most recent surveillance report;[1] at the end of 2016, there were 26,444 people estimated to be living with HIV in Australia. Male to male sexual intercourse continues to be the major HIV risk exposure in Australia, reported for 712 (70%) HIV diagnoses in 2016; heterosexual sexual intercourse reported for 209 (21%) diagnoses; both male to male sexual intercourse and injecting drug use for 51 (5%) diagnoses; and injecting drug use for 14 (1%) diagnoses. In 2016, the HIV prevalence, or the proportion of all people in Australia who were living with HIV, was 0.13%, which is low compared to other high income countries and to countries in the Asia-Pacific region. Based on the test for immune function (CD4 T lymphocyte (CD4+) cell count), a third (33%) of new HIV diagnoses in 2016 were classified as late diagnoses (CD4+ cell count of < 350 cells/μL). These diagnoses are likely to have been in people who had acquired HIV at least four years before diagnosis without being tested.

Anti-retroviral therapy (ART) has reduced HIV-related morbidity and mortality at all stages of HIV infection and has reduced HIV transmission. Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4+ cell numbers and confers substantial clinical benefits, all of which are important treatment goals. HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in HIV-infected cohorts. Despite these benefits, eradication of HIV infection cannot be achieved with available anti-retroviral (ARV) drugs. Treatment interruption has been associated with rebound viremia, worsening of immune function and increased morbidity and mortality. Thus, once initiated, ART should be continued, with the following key treatment goals:

- Maximally and durably suppress plasma HIV ribonucleic acid (RNA);
- Restore and preserve immunologic function; and
- Reduce HIV-associated morbidity and prolong the duration and quality of survival and prevent HIV transmission.

It is now known that the most effective way to treat HIV is by combining different classes of drugs that attack the virus in different ways. HIV treatments are grouped by class according to the stage of the HIV life cycle that they block. The entry inhibitors are a class of ARV drugs that prevents HIV from entering the CD4 cell. The reverse transcriptase inhibitors inhibit the enzymes that convert the genetic material of HIV from RNA into

[1] Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual surveillance report 2017. Sydney: Kirby Institute, UNSW Sydney; 2017

deoxyribonucleic acid (DNA) making it compatible with human DNA. Once this stage is complete, HIV DNA is then inserted or integrated into the DNA of the CD4 cell and treatments that block this stage of HIV replication are called integrase inhibitors. Once HIV DNA enters the nucleus of the CD4 cell (integration), the CD4 cell becomes a sort of HIV factory that produces building blocks for new HIV. Protease inhibitors prevent viral replication by selectively binding to viral protease which normally cuts long chains of HIV proteins into smaller individual proteins (new HIV cannot be made when HIV protease does not work properly).

Achieving viral suppression of HIV-1 infection currently requires the use of combination ARV regimens that generally include three active drugs from two or more drug classes. Current treatment guidelines recommend the lifelong use of 3 drugs to construct a complete regimen for the treatment of HIV, usually a 2 drug nucleoside reverse transcriptase inhibitor (NRTI) backbone plus a third drug in a non-NRTI class (for example, integrase strand transfer inhibitor (INSTI), protease inhibitor, or non-nucleoside reverse transcriptase inhibitor (NNRT)). When initial HIV suppression is not achieved or not maintained, changing to a new regimen with at least two active drugs is often required. The increasing number of ARV drugs and drug classes makes viral suppression below detection limits an achievable goal in most patients. There have been no randomised trials addressing the question of when to start antiretroviral therapy or the choice of initial or second-line therapy for HIV-2 infection; thus, the optimal treatment strategy has not been defined.

Dolutegravir (DTG) is a potent dual cation binding INSTI, exhibiting rapid reduction in viral load, best in class efficacy and a high barrier to resistance. In addition, due to its mechanism of metabolism, DTG lacks many of the frequent drug interactions associated with other medications commonly taken by HIV-positive patients (specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants). To date, the efficacy pharmacokinetics (PK), safety and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to IIIb clinical trials.[2,3]

Lamivudine (3TC) is a potent cytidine nucleoside analogue in the NRTI class of drug with a favourable long-term safety profile. Available since 1995 as a single agent (3TC);[4,5] it is also available as part of two backbone fixed dose combination (FDC) products (zidovudine (ZDV)/3TC, under the product name Combivir; and abacavir sulfate (ABC)/3TC, under the product names Epzicom/Kivexa). Although 3TC monotherapy is known to select for resistance due to a single point mutation that reduces antiviral activity, it is predicted that 3TC, when combined with DTG with its high barrier to resistance and ability to confer a very rapid decline in HIV-1 RNA, may be less likely to select for resistance consistent with clinical studies combining DTG, 3TC and ABC.

DTG + 3TC is a 2 drug regimen of 2 potent, well-characterised and well-tolerated ARVs that may provide a novel 2 drug first-line regimen with effective antiviral suppression while limiting the risk of adverse reactions by having one less ARV in the regimen. The combination of 3TC with DTG, with its high barrier to resistance and ability to confer a rapid decline in HIV-1 RNA, may have a low risk of selecting for resistance that is comparable overall to 3 drug regimens.

[2] Tivicay (dolutegravir) Summary of Product Characteristics, July 2018. Available from the United Kingdom electronic medicines compendium website. Accessed 4 September 2018.
[3] Tivicay (dolutegravir) US Prescribing Information, November 2017. Available from the GlaxoSmithKline website Accessed 4 September 2018.
[4] Epivir (lamivudine) Summary of Product Characteristics, March 2018. Available from the United Kingdom electronic medicines compendium website. Accessed 4 September 2018
[5] Epivir (lamivudine) US Prescribing Information, April 2018. Available from the GlaxoSmithKline website Accessed 4 September 2018

Regulatory status

Dovato is a new combination of previously approved active ingredients for Australian regulatory purposes.

Dovato contains:

- Dolutegravir (DTG), a HIV INSTI registered in Australia in 2014 (registered as Tivicay 50 mg; ARTG 205212); and
- Lamivudine (3TC) (registered as 3TC 150 mg and 300 mg; ARTG 54313 and 81359), a NRTI.

At the time the TGA considered this application, a similar application had been approved the European Union (EU; approved on 1 July 2019) and the USA (approved on 8 April 2019) and was under consideration in Canada and Switzerland (Table 1).

Table 1: International regulatory status of Dovato as of 11 July 2019

Region	Submission date	Status	Indication
European Union	17 September 2018	Approved 1 July 2019	*Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine*
USA	18 October 2018	Approved 8 April 2019	*Dovato, a two-drug combination of dolutegravir (integrase strand transfer inhibitor (INSTI)) and lamivudine (nucleoside analogue reverse transcriptase inhibitor (NRTI)) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato.*
Canada	20 September 2018	Under review	Under review
Switzerland	19 October 2018	Under review	Under review

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 website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-04002-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 October 2018
First round evaluation completed	5 April 2019
Sponsor provides responses on questions raised in first round evaluation	30 April 2019
Second round evaluation completed	17 June 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	27 June 2019
Sponsor's pre-Advisory Committee response	11 July 2019
Advisory Committee meeting	1-2 August 2019
Registration decision (Outcome)	11 September 2019
Completion of administrative activities and registration on ARTG	16 September 2019
Number of working days from submission dossier acceptance to registration decision*	201

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

The drug product is a FDC, immediate release, tablet for oral administration containing 52.6 mg dolutegravir sodium, which is equivalent to 50 mg dolutegravir (free acid), and 300 mg lamivudine.

DTG/3TC tablets, 50 mg/300 mg, are oval (approximately 18.5 x 9.5 mm), biconvex, white, film coated tablets, debossed with 'SV 137' on one face.

The tablets are packed in an opaque, white, round, high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure that includes a polyethylene faced induction seal liner.

First round evaluation recommendations

The provisional ARTG record should be amended to replace the entry for dolutegravir in the formulation with dolutegravir sodium 52.6 mg.

Subject to provision of data demonstrating compliance with a tighter dissolution limit and earlier sampling time and evidence that the test methods for related substances are capable of detecting and quantifying all potential degradants, the stability data provided support the proposed shelf-lives of 24 months when stored below 30 °C in commercial packaging and [Information redacted].

Subject to satisfactory resolution of issues raised, ethics committee approval and the long-term stability of the analytes, the results of the pivotal bioequivalence study support the conclusions that in the fasted state, the formulation proposed for registration is equivalent to co-administration of the single-active products with respect to dolutegravir area under the plasma concentration time curve (AUC) and maximum observed concentration (C_{max}) and lamivudine AUC but lamivudine C_{max} is approximately 30% higher, and that the effect of administration of the tablet with a high-fat meal is comparable to the reported effects of food on the single-active products.

A number of significant deficiencies in the application data were identified during the assessment.[6] Registration of the product for distribution in Australia is not recommended until each of TGA questions are satisfactorily resolved.

Second round evaluation recommendations (post response to TGA questions)

Responses provided to the TGA questions raised are considered acceptable, except for the following:

- The label should be revised to include the statement 'Store in original package';
- An updated Good Manufacturing Practice (GMP) clearance for one manufacturing site is outstanding and should be provided.

Post-second round evaluation recommendations

The GMP issue is resolved. Noting the sponsor has acknowledged the above label issue and provided an undertaking that it will be addressed in the next data submission, registration of the proposed dolutegravir (as sodium) 50 mg / lamivudine 300 mg FDC tablet under the tradename 'Dovato' is recommended, with respect to pharmaceutical chemistry aspects.

Nonclinical

The nonclinical dossier was of adequate scope and quality. Older studies not previously submitted and new pharmacology, pharmacokinetics/drug interaction studies for DTG or 3TC were provided. No new animal studies were submitted to support efficacy and safety of the proposed combination. This is acceptable as combination therapy (INSTI + NRTI) is established for the proposed indication and a triple combination consisting of DTG, 3TC and abacavir has already been approved.

Safety pharmacology studies not previously submitted showed no new safety concerns.

A new pharmacokinetic distribution study showed very low binding to brain tissue, consistent with earlier reports (Tivicay (dolutegravir) Submission PM-2012-04124-1-2) of low tissue:blood C_{max} ratios for rat brain (≤ 0.17) and absence of central nervous system (CNS) toxicity in rats. A new permeability study with the DTG + 3TC drug combination using Caco-2 cells indicated no significant effect of DTG on 3TC absorptive permeability (that is, there was no interaction at the P-glycoprotein (P-gp) transporter).

[6] These issues were subsequently resolved in the sponsor's response to TGA questions.

In vitro and/or *in vivo* studies demonstrated 3TC is a substrate and a weak inhibitor of renal organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1) and/or multidrug and toxin extrusion protein 2K (MATE-2K) transporters.

As 3TC is a substrate of OCT2 and DTG is a known inhibitor of OCT2, human plasma levels of 3TC for the combination may be higher than levels in patients taking 3TC alone. However, since DTG and 3TC have already been administered to patients in the FDC Triumeq, clinical data on potential pharmacokinetic interactions between DTG and 3TC in patients should be available. Pharmacokinetic drug interactions are not expected with 3TC as the perpetrator at OCT2 and MATE transporters at the anticipated clinical exposure levels.

The applicant did not submit any toxicity studies with the proposed combination. The justification for the absence of such data is based on a lack of common target organs for the two individual components. Both drugs are approved as individual drugs and in other combination products including Triumeq. Each has a long-standing history of clinical use. The sponsor's justification for not conducting combination toxicity studies is acceptable.

Older studies on mitochondrial toxicity were unremarkable, consistent with previously reported studies.

Pregnancy category

Pregnancy Category B1 is proposed.[7] However, Pregnancy Category B3;[8] is considered appropriate based on the Pregnancy categories for the individual agents (B1 and B3 for DTG and 3TC, respectively).

Overall conclusion

There are no objections on nonclinical grounds to the registration of Dovato.

Clinical

The DTG/3TC FDC development program consisted of:

- Two pivotal clinical efficacy and safety studies: Study 204861 (the GEMINI-1 trial) and Study 205543 (the GEMINI-2 trial).
- One pivotal PK study: Study 204994 examined the bioequivalence between FDC tablet formulations and the free combination. In addition, the effect of a high fat meal on exposure was examined.
- One supporting PK study: Study 204993 evaluated the relative bioavailability of two experimental DTG/3TC FDC tablet formulations versus co-administration of the single entity products.

The GEMINI trials were conducted with the DTG and 3TC separate co-administered entities; Study 204994 formed the pharmacokinetic (PK) bridge to the GEMINI trials.

[7] 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.
[8] Pregnancy Category B3: 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 shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Additionally, key studies from the single entity clinical development programs (previously evaluated) were referenced.

No studies examined the pharmacodynamics (PD) of the proposed FDC formulation or the population PKs.

Adolescent patients were not included in the GEMINI trials. However, there is an agreed European Medicines Agency (EMA) Paediatric Investigation Plan (PIP). Adolescents paediatric data (aged 12 to 17 years) were available in prior studies for the individual components.

Pharmacology

Pharmacokinetics (PK)

Study 204994

Study 204994 was a pivotal Phase I, open label, randomised, bioequivalence study. Study 204994 examined the bioequivalence between FDC tablet formulations and the free combination and food effect (fasted and fed state) in healthy volunteers.

The proposed FDC tablet formulation and the free combination were bioequivalent under fasted conditions in regard to the area under the plasma concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the plasma concentration time curve from time zero to the last quantifiable time point ($AUC_{0\text{-}t}$) and C_{max} of DTG and the $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ of 3TC (geometric least squares mean ratio 90% confidence interval (CI) between 0.8 to 1.25), but not for 3TC C_{max} which was 31.8% higher for the proposed FDC compared to the reference formulation. However, that 3TC C_{max} value outside the margin is unlikely to be of clinical significance.

A high fat meal resulted in a modest increase (approximately 32%) in DTG $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ and in a modest decrease in 3TC C_{max} of approximately 30%.

Study 204993

Study 204993 was a supporting study. Study 204993 evaluated the relative bioavailability of two experimental DTG/3TC FDC experimental tablet formulations versus co-administration of the single entity products. However, the experimental formulation is not proposed for marketing.

Evaluator conclusions

The conduct of the single study that was provided in support of the current submission was satisfactory, the data analyses undertaken were appropriate and the analytical methods used to measure exposure levels were validated.

The proposed PI appears to accurately incorporate the new data for the FDC into the existing information regarding DTG and 3TC.

Population PK data (popPK)

No data submitted.

Pharmacodynamics (PD)

No data submitted.

Efficacy

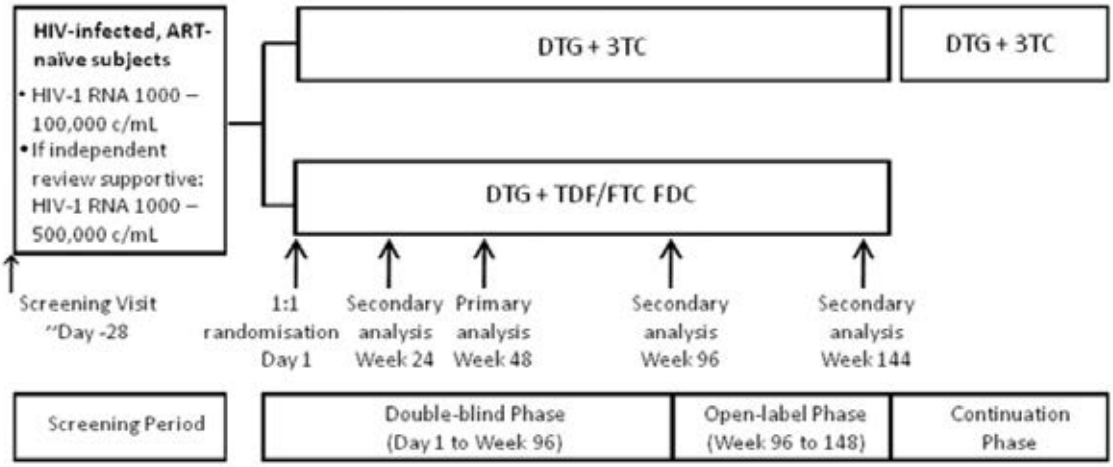
Study 204861 (GEMINI-1 trial) and Study 205543 (GEMINI-2 trial)

Design

Data from 2 ongoing pivotal, identical, Phase III, randomised, parallel group, double blind, 148 week non-inferiority studies provided the main evidence to support antiviral activity

of DTG 50 mg plus 3TC 300 mg once daily compared to DTG plus the FDC tablet of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) once daily in 1441 ART-naïve (defined as ≤ 10 days of prior therapy with any ART agent following a diagnosis of HIV-1 infection) adult subjects with HIV-1 infection. The study initially enrolled subjects with a screening HIV-1 RNA of 1000 to ≤ 100,000 copies per millilitre (c/mL), but the viral load cap was increased during the study to ≤ 500,000 c/mL.

Figure 1: GEMINI 1 and 2 trials; study schematic



Target enrollment N=700 randomized subjects planned/study. Subjects randomized 1:1 to receive a 2-drug regimen of DTG + 3TC once daily or DTG + TDF/FTC FDC once daily. Randomization was stratified by Screening HIV-1 RNA (≤ or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

Subjects with pre-existing viral resistance (based on the presence of any major resistance-associated mutation), severe hepatic/renal impairment and hepatitis B positive or requiring hepatitis C therapy or with significant suicidality risk were excluded from both pivotal studies. HIV-2 infected subjects were not evaluated.

Although adolescents were not included in the pivotal GEMINI trials, both Tivicay (dolutegravir) and 3TC (lamivudine) are approved in combination with other ARV agents for the treatment of HIV-1 infection in adults and adolescents. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are approved doses for adolescents ≥ 12 years of age weighing ≥ 40 kg (DTG) or for paediatric patients weighing ≥ 25 kg (3TC). Prior studies have shown that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults and supports extrapolation of GEMINI trial efficacy data to adolescents (Table 3).

Table 3: Summary of supportive single entity (SE) studies for efficacy

Study	Study Title	SE Study Efficacy Conclusions
ING114467 (SINGLE) (DTG) GSK Document Number: 2014N196290_01 Status: Week 144 and End-of-Study CSRs Complete	A Phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects	**At Week 48**, 88% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 81% of participants on the single tablet regimen Atripla [difference and 95% CI; 7.4% (+2.5% to +12.3%); difference in the primary endpoint was statistically significant, p=0.003]. **At Week 96**, 80% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 72% of participants on the single tablet regimen Atripla [difference and 95% CI; 8.0% (+2.3% to +13.8%); difference in the primary endpoint was statistically significant, [p=0.006]. Response rates on DTG+ ABC/3TC and Atripla were generally consistent across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. **At Week 144**, 71% of study participants in the DTG + ABC/3TC treatment group were virologically suppressed (<50 c/mL) versus 63% of participants on the single tablet regimen of Atripla [adjusted difference and 95% CI; 8.3% (+2.0% to +14.6%); difference in the primary endpoint was statistically significant, [p=0.010]; therefore, statistical superiority at Week 144 was maintained. Differences in the Snapshot analysis were primarily driven by a lower rate of discontinuation due to AEs in the DTG + ABC/3TC treatment group. Response rates were similar between the DTG + ABC/3TC and the Atripla treatment groups across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. The longer-term end-of-study data support the safety of DTG in combination with ABC/3TC once daily in an HIV-infected treatment-naive patient population. The majority of subjects receiving DTG + ABC/3TC FDC who entered the continuation phase past Week 144 maintained viral suppression, based on an observed analysis. In the DTG + ABC/3TC FDC arm, antiviral response was sustained with 93% (193/207) of subjects with HIV-1 RNA <50 c/mL at Week 156 based on the observed data. The data from this completed study continue to support the use of DTG 50 mg + ABC/3TC once daily for the management of HIV infection in INSTI-naive subjects.
ING113086 (SPRING-2) (DTG) GSK Document Number: 2013N158737_01 Status: Week 96 CSR and End-of-Study CSRs Complete	A Phase III, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in	**At Week 48**, 88% of study participants in the DTG arm versus 85% of participants in the RAL arm were virologically suppressed (HIV-1 RNA <50 c/mL) [difference and 95% CI; 2.4% (-2.2, 7.1)]. This demonstrated DTG is non-inferior to RAL at Week 48, because the lower end of the 95% CI for the treatment difference (-2.2%) is greater than the pre-specified non-inferiority margin of -10%. DTG performed as well as RAL regardless of baseline viral load, background dual NRTI, demographic subgroups, HIV risk factors, baseline CD4+ cell count and baseline CDC category. **At Week 96**, the proportion of subjects with HIV RNA <50 c/mL (81%) compared favorably with RAL (76%) through 96 weeks. DTG performed as well as RAL regardless of baseline viral load or background dual NRTI. DTG
NUCA3002 (3TC) Glaxo Document Number UCR/95/003 Randomized, double-blind Status: Complete	A randomized 3TC, ddC double-blind (ZDV open-labelled) multicenter trial to evaluate the safety and efficacy of 3TC (150 mg low dose) administered concurrently with ZDV versus 3TC (300 mg high dose) administered concurrently with ZDV versus dideoxycytidine (ddC) administered concurrently with ZDV in the treatment of HIV-1 infected ZDV-experienced (≥24 weeks) study participants with CD4+ cell counts of 100-300 cells/mm³	**At Week 24**, high- and low-dose ZDV+3TC combination therapies produced similar and sustained absolute and percent CD4+ cell count increases, and decreases in ICD p24 antigen, ~2-microglobulin, and neopterin, all of which were superior to those of ZDV+DDC (0.75 mg). ZDV+3TC (300 mg) effected statistically significantly greater 10gl0 HIV-I RNA reductions relative to the ZDV+DDC (0.75 mg) group, however ZDV+3TC (150 mg) did not. In general, marker responses for patients who completed 24 weeks of treatment were superior to those of patients who permanently discontinued study drug prior to 24 weeks. Both ZDV+3TC therapies provided superior CD4+ and 10gl0 HIV-I RNA effects regardless of age, gender, or race, relative to ZDV+DDC (0.75 mg) however, Caucasians exhibited higher CD4+ cell count values and lower HIV-I RNA values than did Non-Caucasians.
NUCB3002 (3TC) Glaxo Report Number GIO/94/005 Randomized, double-blind Status: Complete	A randomized, controlled, Lamivudine (3TC) double-blinded trial to compare the safety and efficacy of ZDV monotherapy versus Lamivudine plus ZDV in combination in treating HIV-1 infected patients who are ZDV Therapy-experienced with a CD4+ cell counts between 100 cells/mm³ to 400 cells/mm³	**At Week 24**, efficacy was measured using both immunological parameters (CD4+ count, p2-microglobulin, neopterin) and measures of viral load (HIV-I p24 antigen, HIV-I RNA PCR, plasma viral load, cellular viremia). The combination of 3TC (150mg or 300mg BID) and ZDV (200mg TID) showed significantly greater and more sustained responses over ZDV monotherapy in immunological and viral load parameters measured over the 24 week study period. No significant differences were shown between the two doses of 3TC (150 mg BID or 300 mg BID) in combination with ZDV. Note: After 24 weeks, study participants were eligible to enter NUCB3002c, a rollover trial.
Adolescent Extrapolation GSK Document Number 2018N363795_00 Status: Complete	Adolescent Extrapolation report for GSK3515864	Week 24 analysis of GEMINI-1 and GEMINI-2 Phase III studies conducted with the single entity tablets Tivicay and Epivir showed that DTG plus 3TC is highly efficacious and well tolerated in HIV-infected, ART-naive patients. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are adult doses that have already been authorized as individual agents in adolescents ≥12 years of age weighing ≥40 kg (DTG) or in pediatric patients weighing ≥25 kg (3TC). The available PK data from pediatric subjects (both observed and modelled), including adolescents ≥ 12 to <18 years, demonstrate that DTG and 3TC exposures are sufficiently similar to adults to permit extrapolation of efficacy data from pharmacokinetic correlation. The data from pivotal BE Study 204994, combined with data from the 3TC historical studies, provides an acceptable PK bridge to the single entities used in GEMINI-1 and GEMINI-2 Phase III trials, ensures similarity in terms of safety and efficacy and supports the adolescent indication for the DTG/3TC FDC product. The totality of evidence supports the rationale of an extrapolation approach from adults to adolescents and from the individual DTG plus 3TC to the DTG/3TC FDC. The DTG/3TC 50mg/300mg FDC is recommended as a once-daily complete regimen administered with or without food for the treatment of HIV-1 infection in ART-naive adolescents (.12 years to <18 years of age, weighing at least 40 kg).

Both pivotal studies complied with TGA-adopted Committee for Medicinal Products for Human Use (CHMP) guidelines for evaluation of medicinal products for treatment of HIV

infection.[9] Minor Good Clinical Practice (GCP) compliance issues in the GEMINI-1 trial and HIV-1 sssay contamination and reagent issues in both studies were observed.

GEMINI-1 trial results

In the GEMINI-1 trial (Intent to treat exposed (ITT-E) analysis), 90% of subjects in the DTG + 3TC group and 93% of subjects in the DTG + TDF/FTC group achieved the primary efficacy endpoint of plasma HIV-1 RNA < 50 c/mL at Week 48 (snapshot algorithm). Based on a 10% non-inferiority margin, the efficacy analysis demonstrated non-inferiority of DTG + 3TC compared to DTG + TDF/FTC at Week 48 (adjusted treatment difference (95% CI) = -2.6% (-6.7%, 1.5%)).

The results for the Per protocol (PP) and Intent to treat (ITT) populations were supportive of those from the ITT-E (primary) population. Treatment differences across demographic (age, race and gender) subgroups and baseline HIV-1 RNA viral load support the primary endpoint (HIV-1 RNA <50 c/mL at Week 48). There was a lower response rate in the DTG + 3TC arm in subjects with lower Baseline CD4+ cell counts.

GEMINI-2 trial results

In the GEMINI-2trial (ITT-E analysis), 93% of subjects in the DTG + 3TC group and 94% of subjects in the DTG + TDF/FTC group achieved the primary efficacy endpoint of plasma HIV-1 RNA < 50 c/mL at Week 48 (snapshot algorithm). Based on a 10% non-inferiority margin, the efficacy analysis demonstrated that DTG + 3TC was non-inferior to DTG+TDF/FTC at Week 48 (adjusted treatment difference (95% CI) = -0.7% (-4.3%, 2.9%)).

The results for the PP population and ITT populations were supportive of those from the ITT-E (primary) population. Treatment differences across demographic (age, race and gender) subgroups support the primary endpoint (HIV-1 RNA < 50 c/mL at Week 48).

Across both the baseline HIV-1 RNA subgroup and the baseline CD4+ cell count subgroup, there was statistically significant evidence of heterogeneity for the difference in proportion of subjects with HIV-1 RNA < 50 c/mL. This appears to be driven by a higher response rate in the DTG+3TC group and a lower response in the DTG+TDF/FTC group in the subjects with higher baseline plasma HIV-1 RNA (> 100,000 c/mL). In the subgroup of subjects with lower baseline CD4+ cell count, there was a lower response rate for subjects receiving DTG+3TC.

[9] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guidelines for evaluation of medicinal products for treatment of HIV infection, EMEA/CPMP/EWP/633/02 Rev. 3, 28 April 2016.

Table 4: GEMINI trials (Studies 204861 and 205543; and pooled studies)' Proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 48 (ITT-E population)

Treatment	Number Responded/ Total Assessed n/N (%)	Difference in Proportion, % (95% CI)[a]	Adjusted Difference in Proportion, % (95% CI)[b]
204861			
DTG + 3TC	320/356 (90)	-2.8 (-7.0, 1.3)	-2.6 (-6.7, 1.5)
DTG + TDF/FTC FDC	332/358 (93)		
205543			
DTG + 3TC	335/360 (93)	-0.8 (-4.4, 2.8)	-0.7 (-4.3, 2.9)
DTG + TDF/FTC FDC	337/359 (94)		
Pooled			
DTG + 3TC	655/716 (91)	-1.8 (-4.6, 0.9)	-1.7 (-4.4, 1.1)
DTG + TDF/FTC FDC	669/717 (93)		

Data Source: 204861 Table 2.1, Study 205543 Table 2.1, GEMINI ISS/ISE Table 2.1.

a. Difference: Proportion on (DTG + 3TC) – Proportion on DTG + TDF/FTC FDC.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤ or >100,000 c/mL) and CD4+ cell count (≤ or >200 cells/mm3). Pooled analysis also stratified by study.

Table 5: GEMINI trials (Studies 204861 and 205543; and pooled studies) Proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 48 (PP population)

Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion, % (95% CI)[a]	Adjusted Difference in Proportion, % (95% CI)[b]
204861			
DTG + 3TC	317/345 (92)	-2.0 (-5.9, 1.8)	-1.9 (-5.7, 1.9)
DTG + TDF/FTC	325/346 (94)		
205543			
DTG + 3TC	328/349 (94)	-0.8 (-4.2, 2.6)	-0.7 (-4.1, 2.7)
DTG + TDF/FTC	329/347 (95)		
Pooled Data			
DTG + 3TC	645/694 (93)	-1.4 (-4.0, 1.1)	-1.3 (-3.9, 1.2)
DTG + TDF/FTC	654/693 (94)		

Data Source: 204861 Table 2.2, Study 205543 Table 2.2, GEMINI ISS/ISE Table 2.2.

a. Difference: Proportion on DTG + 3TC – Proportion on DTG + TDF/FTC.

b. Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study.

Pooled analysis

A pooled analysis of the GEMINI trials was also conducted. The subject disposition, baseline demographics and disease characteristics for the pooled GEMINI trials was similar to that described for the individual studies. The results of the pooled analysis for the primary efficacy endpoint of proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 48 (snapshot analysis) were similar to the results observed in the individual studies (see Table 4); overall response rate was 91% (655 out of 716) and 93% (669 out of 717) in the DTG+3TC and DTG + TDF/FTC treatment groups, respectively.

The results for the PP population (see Table 5) and ITT Populations were supportive of those from the ITT-E (primary) population.

The secondary endpoint of proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 24 (snapshot analysis) also showed similar results in the pooled analysis. As the lower limit of quantitation detection for the Abbott RealTime HIV-1 Assay used in both pivotal studies was 40 c/mL, an additional sensitivity *post hoc* analysis was carried out for

the proportion of subjects with plasma HIV-1 RNA < 40 c/mL by visit. In the pooled analysis at Week 48, 90% and 92% of subjects receiving DTG + 3TC and DTG + TDF/FTC, respectively, achieved virologic success at the threshold of HIV-1 RNA < 40 c/mL, which represents a 1% reduction in each arm compared to the 91% and 93% of subjects in the ITT-E who achieved virologic success at the HIV-1 RNA <50 c/mL threshold.

Within the individual studies and the pooled analysis, the proportion of subjects with plasma HIV-1 RNA <50 c/mL by visit was high and similar in both treatment groups and most subjects in both arms achieved plasma HIV-1 RNA < 50 c/mL by Week 4 suggesting a rapid and sustained response Kaplan-Meier estimates of the time to viral suppression (HIV-1 RNA <50 c/mL) through Week 48 indicated that subjects reached viral suppression at a similar time point in both treatment groups (median time to viral suppression = 29.0 days).

Few subjects met protocol-defined confirmed virologic withdrawal (CVW) criteria in either treatment group through Week 48. No patients met CVW non-response criteria (decrease in plasma HIV-1 RNA of < 1 $\log_{10}$ c/mL by Week 12, with subsequent confirmation, unless plasma HIV-1 RNA was < 200 c/mL, or confirmed plasma HIV-1 RNA ≥ 200 c/mL on or after Week 24) and < 1% of subjects in both treatment groups met CVW rebound criteria (confirmed rebound in plasma HIV-1 RNA levels to > 200 c/mL after prior confirmed suppression to < 200 c/mL). The incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria was a secondary endpoint in each study. No subject meeting CVW criteria in either group had treatment emergent INSTI or NRTI resistance through Week 48.

CD4+ cell counts increased at each visit in both treatment groups with no significant difference between treatment groups in the change in CD4+ cell counts from Baseline to Week 48 in either study or the pooled analysis. However, in the pooled analysis statistically significant higher increases in the CD4+ cell count were observed in the DTG + 3TC group compared to the DTG + TDF/FTC group at Week 8, Week 12, Week 16 and Week 24.

Heterogeneity of response

In Study 204861 (GEMINI-1 trial), there was no evidence of heterogeneity in the treatment differences in the proportions with plasma HIV-1 RNA < 50 c/mL at Week 48 across the baseline HIV-1 RNA subgroups (< or > 100,000 c/mL) while in Study 205543 (GEMINI-2 trial), there was statistically significant evidence of heterogeneity for the difference in proportion of subjects with HIV-1 RNA < 50 c/mL at the 10% level of significance (p = 0.03), mainly driven by the higher response rate in the DTG + 3TC group, and lower response rate in the DTG + TDF/FTC group in the subgroup of subjects with baseline plasma HIV-1 RNA > 100,000 c/mL. However, in the pooled analysis, no statistically significant evidence of heterogeneity between the combinations of baseline HIV-1 RNA subgroups (<or > 100,000 c/mL) and studies was observed for the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (see Table 6).

While the Screening HIV-1 RNA viral load for subjects participating in Study 204861 and Study 205543 was capped at <500,000 c/mL, 28 subjects had a baseline HIV-1 RNA > 500,000 c/mL (DTG+3TC, 13 subjects; DTG+TDF/FTC, 15 subjects). 11 of 13 subjects (85%) in the DTG+3TC group and 12 of 15 (80%) subjects in the DTG+TDF/FTC group had plasma HIV-1 RNA <50 c/mL at Week 48.

In each study, in the baseline CD4+ cell count <200 cells/mm^3 subgroup, there was a lower response rate in the DTG+3TC group compared to the DTG+TDF/FTC group, although the test for heterogeneity for an effect of baseline CD4+ cell count (<200 or >200 cells/mm^3) on the treatment difference in the proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 48 was only significant in Study 205543. In the pooled analysis, there was statistically significant evidence of heterogeneity at the 10% level (p = 0.10) across

baseline CD4+ cell count levels and Study on the treatment difference in proportion of subjects with HIV-1 RNA <50 c/mL, indicating that the difference in response rates between treatments was not consistent across baseline CD4+ cell count categories (< or > 200 cells/mm^3) and study (see Table 6).

Post-baseline changes in CD4+ cell counts were similar between the treatment arms across categories of baseline plasma HIV-1 RNA and CD4+ cell count in the pooled analysis.

A summary of numerical results and analysis is shown in Table 6.

Table 6: GEMINI trials (separate studies and pooled populations); Tests of heterogeneity for the proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 48 by baseline randomisation strata (ITT-E Population)

	DTG + 3TC n/N (%)	DTG + TDF/FTC n/N (%)	Difference in Proportion % (95% CI)
Study 204861[a]			
HIV-1 RNA ≤100,000 c/mL	255/282 (90)	263/282 (93)	-2.8 (-7.3, 1.7)
HIV-1 RNA >100,000 c/mL	65/74 (88)	69/76 (91)	-3.0 (-12.8, 6.9)
Test of Heterogeneity[b]			**p = 0.98**
CD4+ cell count ≤200 cells/mm^3	25/31 (81)	26/29 (90)	-9.0 (-26.8, 8.8)
CD4+ cell count >200 cells/mm^3	295/325 (91)	306/329 (93)	-2.2 (-6.4, 1.9)
Test of Heterogeneity[b]			**p = 0.47**
Study 205543[a]			
HIV-1 RNA ≤100,000 c/mL	271/294 (92)	268/282 (95)	-2.9 (-6.8, 1.1)
HIV-1 RNA >100,000 c/mL	64/66 (97)	69/77 (90)	7.4 (-0.6, 15.3)
Test of Heterogeneity[b]			**p = 0.03**
CD4+ cell count ≤200 cells/mm^3	25/32 (78)	25/26 (96)	-18.0 (-34.1, -1.9)
CD4+ cell count >200 cells/mm^3	310/328 (95)	312/333 (94)	0.8 (-2.8, 4.4)
Test of Heterogeneity[b]			**p = 0.03**
Pooled Analysis (Study 204861 and Study 205543)[c]			
Baseline HIV-1 RNA			
HIV-1 RNA ≤100,000 c/mL	526/576 (91)	531/564 (94)	-2.8 (-5.9, 0.2)
HIV-1 RNA >100,000 c/mL	129/140 (92)	138/153 (90)	2.1 (-4.4, 8.5)
Test of Heterogeneity[b]			**p = 0.14**
Baseline CD4+ cell count			
CD4+ cell count ≤200 cells/mm^3	50/63 (79)	51/ 55 (93)	-13.4 (-25.5, -1.3)
CD4+ cell count >200 cells/mm^3	605/653 (93)	618/662 (93)	-0.7 (-3.5, 2.1)
Test of Heterogeneity[b]			**p = 0.10**

Data Source: Study 204861 Table 2.7, Study 205543 Table 2.7, GEMINI ISS/ISE Table 2.7.

a. Proportion on DTG + 3TC - Proportion on DTG + TDF/FTC.

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata and study.

c. Difference: Proportion on DTG + 3TC - Proportion on DTG + TDF/FTC; data combined across studies using a Cochran-Mantel Haenszel stratified analysis.

Viral loads/virological failure

Stratified viral load data (for example, 20 to 49, 50 to 99, 100 to 199, 200 to 400 and > 400 copies/mL) (for the pooled GEMINI studies) are shown in Table 7. No significant differences were shown between the DTG+3TC and the DTG + TDF/FTC arms.

Table 7: Pooled GEMINI trials, summary of study outcome (< 50 c/mL) at Week 48 by plasma HIV-1 RNA categories (ITT-E population)

	Pooled week 48	
	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Plasma HIV-1 RNA <50 c/mL	655 (91)	669 (93)
Plasma HIV RNA >=50 c/mL Data in window not below threshold Discontinued for lack of efficacy Discontinued for other reasons and HIV-1 RNA ≥50 c/mL	**20 (3)**	**13 (2)**
>=50,<100	9 (1%)	5 (<1%)
>=100, <200	3 (<1%)	2 (<1%)
>=200, <400	2 (<1%)	1 (<1%)
>=400	4 (<1%)	4 (<1%)
Change in ART	2 (<1)	1 (<1)
No Virologic Data in window; Discontinued due to AE/death Discontinued, Other reasons Missing window data, on study	**41 (6)**	**35 (5)**
Last HIV-RNA in study, copies/ml:		
<50	37 (5%)	27 (4%)
>=50,<100	0	1 (<1%)
>=100, <200	0	0
>=200, <400	0	0
>=400	0	0
No on-treatment VL	4 (<1%)	7 (<1%)

Other efficacy studies

Previously submitted studies from DTG or 3TC SE development programs were also provided to support this application and are categorised as supportive studies. Key study design and efficacy results are summarised in Table 3.

Evaluator commentary on the other efficacy studies: the supportive SE studies provided data that may be included in labelling for Dovato, and were conducted during the individual agent (DTG and 3TC) development programs. Key clinical studies were described in the submitted dossier summaries and clinical study reports (CSR) for these studies have been previously submitted and evaluated. These studies are not essential for the benefit-risk assessment of the proposed FDC of DTG+3TC, but are considered helpful and supportive for the proposed indication.

Safety

The safety assessment of Dovato in HIV-1 infected treatment-naïve adult subjects with viral load ≤ 500,000 HIV-1 RNA copies/mL, is based on the pooled primary Week 48 analyses of data from 2 identical, multicentre, double blind, controlled trials, GEMINI-1 and GEMINI-2.

Exposure

Across the 2 GEMINI trials, 1433 subjects were exposed to DTG 50 mg. 716 subjects received at least 1 dose of DTG+3TC and 717 subjects received at least 1 dose of DTG + TDF/FTC.

The extent of exposure to proposed combination treatment with DTG+3TC was adequate to evaluate safety of Dovato in proposed indication.

Overall adverse event profile

Overall, the adverse event (AE) incidence was slightly lower in the DTG+3TC group compared to the DTG+TDF/FTC group (DTG+3TC versus DTG+TDF/FTC: 76% versus 81%). The most commonly reported AE were headache (10% versus 10%), diarrhoea (9% versus 11%), nasopharyngitis (8% versus 11%), upper respiratory tract infection (8% versus 6%), nausea (4% versus 7%), insomnia (4% versus 6%) and pharyngitis (5% versus 4%). The proportions of subjects reporting events were generally similar across the System Organ Classes (SOC) with minor differences observed for some SOCs (for example, gastrointestinal disorders) mainly due to higher reporting in the DTG+TDF/FTC of nausea and diarrhoea.

The majority of AE were Grade 1 (19% versus 21%) or Grade 2 (50% versus 51%) with similar proportions of subjects reporting any Grade 2 to 5 AE in the DTG+3TC and DTG+TDF/FTC groups.

Withdrawal of study drug

In each treatment group, there was a small number of AE leading to withdrawal of study drug; few were considered drug-related.

Deaths and serious adverse events

There were 2 deaths reported up to the Week 48 analysis cut-off (both in the DTG+3TC group) and both were considered unrelated to study drug. The frequency of serious adverse events (SAE) was similar between the treatment groups. There were few drug related SAE reported during the study, with < 1% incidence observed for both treatment groups and no discernible patterns of related events.

Adverse events

Across both DTG-containing treatment groups, the psychiatric AE profile was comparable to the known safety profile for DTG. Psychiatric AEs leading to withdrawal occurred in < 1% of subjects. Suicidal ideation occurred in 1% of subjects in each treatment group, compared with DTG single-entity studies reporting rate of < 1%. Because this rate crossed the 1% threshold, this small numeric change has been represented as a new frequency category within the DTG+3TC prescribing information.

Grade 3 to 4 laboratory toxicities observed at ≥ 1% in the DTG+3TC pooled analysis were identified and compared to the product labels for the individual components. The common Grade 3 to 4 laboratory toxicities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK) and glomerular filtration rate (GFR) observed for the GEMINI trials were consistent with observations from the pivotal studies for the SE studies.

Clinical laboratory assessments demonstrated there were no newly identified laboratory signals of concern in subjects receiving DTG+3TC or DTG+TDF/FTC. The hepatic safety profile of DTG+3TC was consistent with the known profile for the individual single-entity components. Hepatotoxicity has been reported in patients receiving DTG-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations and monitoring of hepatotoxicity is

recommended. There were no reports of cases that met criteria for Hy's law;[10] in the GEMINI trials.

DTG+3TC was associated with lower impact on renal safety parameters compared with DTG+TDF/FTC FDC. At 48 weeks, there were more favourable changes from Baseline in GFR (cystatin C) and urine protein/creatinine ratio in the DTG+3TC group, suggesting that renal function in the DTG+3TC group was better preserved relative to the DTG+TDF/FTC group. Withdrawals from study for renal function related AE or for meeting predefined renal toxicity criteria were more frequently observed in subjects in the DTG+TDF/FTC group compared with the DTG+ 3TC group.

Few subjects experienced changes in lipid profile. A small number of subjects in each treatment group experienced Grade 2 low density lipoprotein (LDL) cholesterol toxicities, with fewer subjects in the DTG+TDF/FTC group; the difference between the 2 treatment groups was statistically significant. However, the total cholesterol/ high density lipoprotein (HDL) ratio category, often used to estimate long-term cardiovascular risk, was generally improved from baseline for both treatment groups.

At Week 48, in the pooled analysis, all markers of bone turnover increased from Baseline in both treatment groups. Larger increases in bone turnover markers were observed in the DTG+TDF/FTC group with a statistically significant difference in favour of the DTG+3TC group. Vitamin D levels declined slightly at Week 48 in the DTG+3TC group and increased slightly in the DTG+TDF/FTC group with a small but statistically significant change in favour of the DTG+TDF/FTC group.

Fewer drug-related AE were reported in the DTG+3TC group (18%) compared with the DTG+TDF/FTC group (24%). This was driven primarily by larger numbers of subjects reporting drug-related Grade 1 events, notably nausea, in the DTG+TDF/FTC group. This could reflect the contribution of a dual NRTI backbone of TDF/FTC versus a backbone of 3TC.

Regimens containing DTG may be associated with a higher rate of immune reconstitution inflammatory syndrome (IRIS) compared with regimens that do not contain an integrase inhibitor, due to faster rate of viral load decline. A total of 39 subjects experienced HIV-associated conditions, AE, or SAE that may be associated with IRIS in the GEMINI trials. Four subjects were adjudicated as having possible IRIS (2 in each treatment group). Serious skin reactions were not observed in the GEMINI trials.

Evaluator conclusions

Over 48 weeks, the safety data from the randomised, double blind Phase III studies comparing DTG+3TC to a standard of care regimen of DTG + TDF/FTC was consistent with the known safety profile for the individual products.

Risk management plan

- The sponsor has submitted European Union Risk Management Plan (EU-RMP) version 0.1 (date not specified; data lock point (DLP) 21 August 2018) and Australian Specific Annex (ASA) version 1 (11 September 2018) in support of this application. In its response to TGA questions, the sponsor has provided updated EU-RMP version 1.0 (date not specified; DLP 21 August 2018) and ASA version 1.1 (17 April 2019). See '*Recommended condition/s of registration*', below.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 8.[11]

[10] Hy's law: ALT > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN.

Table 8: Summary of safety concerns

Summary of safety concerns	Dolutegravir	Lamivudine	Pharmacovigilance		Risk minimisation	
			Routine	Additional	Routine	Additional
Important Identified Risks	Hypersensitivity reactions	-	ü	ü	ü	–
	Hepatobiliary disorders	-	ü	ü	ü	–
Important Potential Risks	Serious rash (DAIDS Grade 3 or 4)	-	ü	ü	ü	–
	Neural tube defects	-	ü†	–	ü	–
Missing Information	Use in pregnancy/ breastfeeding	Use in pregnancy/ breastfeeding	ü	ü§	ü	–
	Long term safety data	Long term safety data	ü	ü‖	–	–

† Specific adverse drug reaction follow-up questionnaire. §Antiretroviral Pregnancy Registry; prospective observational study; cohort and surveillance studies. ‖ Phase III, randomised, double blind, multicentre, parallel group, non-inferiority study.

- During evaluation the sponsor has included 'use in pregnancy/breastfeeding' and 'long term safety data' as missing information for lamivudine. The sponsor has removed 'drug resistance' as an important potential risk for dolutegravir and lamivudine on request of the EMA. The sponsor is requested to include 'serious rash (Division of Acquired Immune Deficiency Syndrome (DAIDS) Grade 3 or 4)' as an important potential risk for dolutegravir in the ASA to align with the EU-RMP.
- The Delegate is requested to review the Pregnancy Category of Dovato with consideration to past classification of lamivudine as Pregnancy Category B3.[8]
- The sponsor has proposed routine pharmacovigilance activities and a specific adverse drug reaction follow up questionnaire to monitor the important potential risk of neural tube defect. The sponsor has proposed a long term safety study and involvement in an Antiretroviral Pregnancy Register. These are acceptable.
- The sponsor has proposed routine risk minimisation activities and has made some amendments to the Consumer Medicines Information (CMI). The sponsor is requested to continue to review the CMI recommendations.

[11] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Recommended condition/s of registration

This cannot be provided as the sponsor is yet to provide a copy of the EU-RMP with sign-off date and information on the dates for PSUR submission in the EU. The sponsor has committed to providing this information prior to registration decision.[12]

Risk-benefit analysis

Delegate's considerations

Discussion

Overall, the 48 week results indicate that the DTG+3TC FDC is effective in the maintenance of plasma HIV-1 RNA < 50 c/mL in ART-naïve adults with HIV-1 infection. This simplified regimen is non-inferior to the 3 drug regimen of DTG+TDF/FTC without an increased risk of virologic failure.

Even though designed as a non-inferiority study, an ITT population was used in the primary analysis. However, the PP population analysis was consistent with the ITT analysis for the primary endpoint.

The main issues of concern were:

- The proposed indication includes non-naïve patients despite the pivotal GEMINI trials being restricted to naïve patients;
- The extrapolation of efficacy and safety data (from the adult GEMINI trials, and the adult and adolescent data from the studies for the individual FDC components) to an adolescent patient population;
- Pregnancy Category B1 is proposed by the sponsor.[7] However, Pregnancy Category B3;[8] is considered appropriate based on the Pregnancy categories for the individual agents (B1 and B3, for DTG and 3TC, respectively).

Proposed indication

Only ART-naïve subjects were evaluated in the pivotal GEMINI studies. Furthermore, only patients with HIV-1 infection were evaluated. The wording of the proposed indication does not clearly state that the proposed FDC is only indicated as first line treatment in ART-naïve patients with HIV-1 infection.

The clinical evaluator raised this in first round clinical evaluation report. The sponsor claimed that the use of Dovato should not be limited to ART-naïve patients and should be available to stable suppressed patients, as long as there was no known or suspected resistance to either antiretroviral component and provided the following information to support this:

- Regulatory requirements as specified in the TGA-adopted CHMP guideline for the evaluation of medicinal products for the treatment of HIV;[9] and alignment of indication in EU positive opinion;
- Australian clinical practice and treatment guidelines;
- TGA accepted approach for extrapolation of data to adolescent patients and historical precedents for use of data in treatment naïve patients to support use in treatment stable, suppressed patients;

[12] The signed EU RMP was subsequently provided by the sponsor.

- Body of data supporting use of dolutegravir plus lamivudine in stable suppressed patients.

The clinical evaluator reviewed the provided information, but retained their indication recommendation to limit treatment with Dovato be limited to HIV-1 infected patients who are ART-naïve. The main reasons were:

- The pivotal studies (GEMINI 1 and 2 trials) were conducted in HIV-1 infected patients with no prior ART;
- The studies provided to support use in stably suppressed HIV-1 infected patients in the response to TGA questions were limited to small, observational studies. The ongoing TANGO trial; a stable switch study in 743 patients currently receiving tenofovir alafenamide fumarate based regimens and randomised to switch to DTG + 3TC or remain on their current regimen, showed comparable efficacy at the 24 week interim analysis: at Week 24, 1 out of 369 (< 1%) subject on the DTG + 3TC arm and 3 out of 372 (< 1%) on the TAF-based regimen arm had a viral load > 50 c/ml in an ITT-E Snapshot Analysis of proportion > = 50 c/mL. There were no confirmed virologic failures in the DTG + 3TC arm and one in the TAF-based regimen arm. The 48 week data is expected in mid-2019 and should also be presented for evaluation when available.
- The US FDA has only approved use of Dovato for treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history. This decision was based on the same dataset that was submitted in Australia.

Fixed dose combination considerations

The efficacy, PK, safety and drug interaction potential of DTG and 3TC as single agents have been evaluated in 2 individual extensive clinical development programs of Phase I to III clinical trials. There appeared to be an absence of a drug-drug interaction between these components.

The bioequivalence (BE) and food effect study (Study 204994) together with the 3TC safety data from historical dose-ranging and registrational studies that evaluated higher 3TC doses/exposures provided an acceptable PK bridge between the DTG/3TC FDC and the DTG + 3TC single entities used in GEMINI-1 and GEMINI-2 trials.

As individual agents, DTG and 3TC are both approved and marketed as Tivicay 50 mg once daily for use in adults and adolescents > 40 kg and 3TC 300 mg once daily for use in adults and children > 25 kg, respectively, the doses used in the current studies (Study 204861 and Study 205543).

Hence, the proposed use of the already approved doses of the individual components of the proposed FDC of DTG and 3TC (Dovato) is justified.

Limitations

Additional to the indication issue described above:

- Stage 3 HIV: There were few subjects with Stage 3 HIV-associated events or disease progressions in both treatment groups, which is not unexpected in the evaluated ART-naïve patient population with a high median CD4+ count. Long term data (once available) could help confirm findings observed after 48 weeks of treatment that adequate virological control provided by both treatments helps limit the development of new Centers for Disease Control and Prevention (CDC) Stage 3 qualifying conditions.
- No data beyond 48 weeks: The current submission only includes 48 week efficacy data for subjects receiving DTG+3TC in the 2 ongoing Phase III GEMINI trial and evidence of long term efficacy beyond 48 weeks is not currently available for the proposed 2 drug

regimen. However, as these studies will continue for 148 weeks, submission of the results on completion should help address this deficiency. Currently, long term data are available only for each of the components from single entity studies. The proposed 2 drug regimen of DTG+3TC was not associated with an increased risk of treatment-emergent resistance, as no subject meeting CVW criteria in either treatment group had treatment emergent INSTI or NRTI resistance through Week 48. The resistance profiles for DTG and 3TC are adequately documented in the current product labelling.

- Adolescent data: Efficacy or safety of DTG+3TC was not evaluated in adolescents. Although adolescents were not included in the pivotal GEMINI studies, both Tivicay (dolutegravir) and 3TC (lamivudine) are approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are approved doses for adolescents' ≥ 12 years of age weighing ≥ 40 kg (DTG) or for paediatric patients weighing ≥25 kg (3TC). Prior studies have shown that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults and allows extrapolation of GEMINI trial data to adolescents (Table 3).
- Pregnancy category and neural tube defects: The sponsor has proposed routine pharmacovigilance activities and a specific adverse drug reaction follow up questionnaire to monitor the important potential risk of neural tube defect. Relevant labelling in the proposed PI is also included to reflect this:
  - In a preliminary analysis of an ongoing birth outcome surveillance study in Botswana there have been 4 cases (as of May 2018) of neural tube defects reported in 426 infants born to mothers who were exposed to dolutegravir-containing regimens from the time of conception. In the same study, no infant born to a woman who started dolutegravir during pregnancy had a neural tube defect, out of 2,812 women. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5 to 1 cases per 1,000 live births. As neural tube defects occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Conclusion

The Delegate agrees with the clinical evaluator's opinion that the overall benefit-risk balance for proposed indication is not favourable for the proposed indication, but would become favourable, if the proposed indication be restricted to ART-naïve patients with HIV-1 infection, as follows:

> *Dovato (dolutegravir/lamivudine) is indicated for the treatment of Human Immunodeficiency Virus-1(HIV-1) infection in treatment-naïve adults and adolescents from 12 years of age weighing at least 40 kg, who have no known or suspected resistance to either antiretroviral component.*

Summary of issues

- The proposed indication includes non-naïve patients despite the pivotal GEMINI trials being restricted to naïve patients;
- The extrapolation of efficacy and safety data (from the adult GEMINI trials, and the adult and adolescent data from the studies for the individual FDC components) to an adolescent patient population;
- Pregnancy Category B1 is proposed by the sponsor.[7] However, Pregnancy Category B3;[8] is considered appropriate based on the Pregnancy categories for the individual agents (B1 and B3 for DTG and 3TC, respectively).

Proposed action

The Delegate has no reason to say, at this time, that the application for Dovato should not be approved for registration for the treatment of HIV-1 infection in treatment-naïve adults and adolescents from 12 years of age weighing at least 40 kg, who have no known or suspected resistance to either anti-retroviral component.

Request for ACM advice

1. The proposed indication that includes non-naïve patients despite the pivotal GEMINI trials being restricted to naïve patients. Can the ACM comment on the proposed inclusion of non-naïve patients?
2. Is the extrapolation of efficacy and safety data (from the adult GEMINI trials, and the adult and adolescent data from the studies for the individual FDC components) to an adolescent patient population appropriate?
3. Pregnancy Category B1 is proposed. However, Pregnancy Category B3 is considered appropriate based on the Pregnancy categories for the individual agents (B1 and B3 for DTG and 3TC, respectively). Can the ACM comment on the appropriate pregnancy category?

Advisory Committee Considerations[13]

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.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Dovato film-coated tablets, containing dolutegravir 50 mg and lamivudine 300 mg.

The ACM considered the following proposed indication:

> *Dovato (dolutegravir/lamivudine) is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age weighing at least 40 kg, who have no known or suspected resistance to either antiretroviral component.*

The ACM agreed that Dovato had an overall positive benefit-risk profile for the revised indication:

> *Dovato (dolutegravir/lamivudine) is indicated for the treatment of Human Immunodeficiency Virus-1 (HIV-1) infection in treatment-naive adults and adolescents from 12 years of age weighing at least 40 kg, who have a baseline viral load < 500 000 copies/mL and no suspected resistance to either antiretroviral component.*

[13] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***The proposed indication that includes non-naïve patients despite the pivotal GEMINI trials being restricted to naïve patients. Can the ACM comment on the proposed inclusion of non-naïve patients?***

The ACM advised that there is currently insufficient data to support the inclusion of non-naïve patients in the indications of Dovato. The ACM expressed concern that there could be an increased incidence of drug resistance in non-naïve patients. The ACM noted that while the 24 week data from the TANGO trial, (a 'switch' study) looked promising, this trial is ongoing. The ACM was of the view that the 'switch' indication should be deferred until the 48 week data from the TANGO trial are available and a formal evaluation of the study is conducted, including an assessment of resistance.

The ACM was of the view that the proposed indication should be revised to more accurately reflect the pivotal trial population.

2. ***Is the extrapolation of efficacy and safety data (from the adult GEMINI trials, and the adult and adolescent data from the studies for the individual FDC components) to an adolescent patient population appropriate?***

The ACM advised that the extrapolation of efficacy and safety data to an adolescent patient population is appropriate. Both single component drugs are approved for use in adolescents and the exposure is similar to that in adults.

3. ***Pregnancy Category B1 is proposed. However, Pregnancy Category B3 is considered appropriate based on the Pregnancy categories for the individual agents (B1 and B3 for DTG and 3TC, respectively). Can the ACM comment on the appropriate pregnancy category?***

The ACM noted that there is no human reproductive data on the combination product; as such, the effect of Dovato on human pregnancy is unknown and evidence for the proposed pregnancy category for Dovato is based on the reproductive data of the single component drugs. The ACM agreed that while there are no particular concerns with the use of lamivudine in pregnancy, there is a potential signal for increased risk of neural tube defects with dolutegravir use at the time of conception. Based on currently available data, it is not yet clear if the rate of neural tube defects is significantly higher than in the general population or in women with HIV on other anti-retroviral combinations, however the ACM was of the view that this is a concern and a cautious approach is warranted. Based on these factors, the ACM advised that Pregnancy Category B3 is considered appropriate.[8]

General advice

In relation to use of Dovato in pregnancy the ACM was of the view that while the absolute risk of birth defects was small, it was still important to include clear warnings in the PI about the potential risk of birth defects including:

- Dovato should be used during the first trimester of pregnancy only if the benefit to the mother outweighs the possible risk to the fetus;
- Women of child-bearing potential should undergo pregnancy testing before initiation of Dovato and Dovato should be avoided in the first 6 weeks of pregnancy (confirmed by ultrasound);
- Women of child bearing potential who are taking Dovato should use effective contraception throughout treatment;
- No studies on the effect of embryofetal development have been conducted with this dolutegravir/lamivudine combination;

- High dose folic acid supplementation is recommended in women of childbearing age taking Dovato if they are pregnant and for the first 12 weeks of pregnancy.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Dovato (dolutegravir (as sodium)/lamivudine) fixed dose combination tablet, indicated for:

> *Dovato (a fixed-dose combination of dolutegravir and lamivudine) is indicated for the treatment of Human Immunodeficiency Virus-1 (HIV-1) infection in antiretroviral treatment-naïve adults and adolescents (from 12 years of age weighing at least 40 kg) who have no known or suspected resistance to either antiretroviral component (see section 5.1 Pharmacodynamic Properties, Clinical trials).*

Specific conditions of registration applying to these goods

The Dovato EU-RMP (version 1.0, dated 10 May 2019, data lock point 21 August 2018), with ASA (version 1.1, dated 17 April 2019), included with submission PM-2018-04002-1-2, 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 Dovato approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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