



THE ROADMAP

The HIV Drug Pipeline and its Patents

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Abbreviations

General

ARV	Antiretroviral drug
CL	Compulsory license
ERP	Global Fund Expert Review Panel
FDC	Fixed-dose combination
LMICs	Low- and middle-income countries
MPP	Medicines Patent Pool
VL	Voluntary license
WHO	World Health Organization

ARV Classes

NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
PI	Protease inhibitor
PK enhancer	Pharmacokinetic enhancer

Existing ARVs*

3TC	Lamivudine
AZT	Zidovudine
ATV	Atazanavir
EFV	Efavirenz
FTC	Emtricitabine
LPV	Lopinavir
NVP	Nevirapine
RTV (or /r)	Ritonavir
TFV	Tenofovir
TD	Tenofovir disoproxil
TDF	Tenofovir disoproxil fumarate

Next-generation / pipeline ARVs

COB	Cobicistat
DRV	Darunavir
DTG	Dolutegravir
ETR	Etravirine
EVG	Elvitegravir
RAL	Raltegravir
RIL	Rilpivirine
TAF	Tenofovir alafenamide fumarate

*WHO-recommended for first- and second-line therapy

Introduction & Methodology

Introduction

What is The Roadmap?

Combating HIV/AIDS in developing countries requires access to the best possible antiretroviral medicines (ARVs). However, when such products are patented – as is typically the case for newly-developed medicines – this can prohibit generic competition and keep prices far beyond the reach of many low- and middle-income countries (LMICs).

The Roadmap is intended to help expand access to the next generation of life-saving ARVs in multiple ways, including: helping treatment activists prioritize efforts and make critical advocacy decisions for the coming years; supporting patent offices, generic producers and procurement agencies in making decisions around ARV patents; and informing policymakers about trends in secondary patenting across this therapeutic class.

The pages that follow summarize clinical, cost, and legal/patent information around key pipeline drugs for HIV/AIDS. Using The Roadmap, advocates can decide which medicines need short- or long-term attention and make informed decisions about the best strategies to pursue, such as patent oppositions, compulsory licenses (CLs), voluntary license (VL) negotiations, and/or direct advocacy.

Why did we create it?

The Roadmap provides the opportunity to be proactive and create a positive agenda in anticipation of medicines that will be relevant for LMICs, which are home to more than 90% of people living with HIV/AIDS⁷ and 97% of all new infections¹⁹. Without an analysis of pipeline products, the global treatment community is left in a position of being reactive to the behavior of originator companies.

In addition, many assume that all pipeline drugs are new and innovative compounds. This research helps assess the level of actual innovation (and therefore patentability) of each product, thereby creating an accurate and comprehensive understanding of the HIV drug pipeline. Assessments of efficacy and inventive step contained herein are based on currently known interpretations of patent law.

Who should use it?

This guide is intended for multiple users, including treatment activists, generic producers, policymakers, patent offices, and procurement agencies, particularly those in the Global South. We also hope our partners in academic and international health institutions will use this information to help further the debate around patent quality, and to make informed decisions about access issues, in order to give a voice to the needs of patients on the ground.

How were the drugs selected?

Out of dozens of pipeline drugs reviewed, we have included 11 in The Roadmap based upon expert opinions as to the most promising drugs for the next generation of HIV/AIDS treatment in LMICs, drawing significantly from recent reports from the Treatment Action Group³, UNITAID⁸, and the Medicines Patent Pool (MPP)². Five of these products are still in the development pipeline, while the remaining six are existing products that are not yet affordable for developing countries.

What information is included?

A 2-3 page profile is provided for each drug. Page 1 provides a high-level overview of the product, including the brand name, proprietor, drug class, stage of development, relevance versus alternatives, patent information (including international patent publication number) and strategies to expand patient access. The following page(s) provide more detailed patent information and are intended for lawyers who are negotiating settlements or licenses, or opposing patents. We focus here on whether a drug product meets legal requirements for inventive step and/or therapeutic efficacy.

We also indicate a level of prioritization for each product based on the likelihood that it will provide a clinical and/or cost advantage to alternatives, as well as an assessment of the base compound's patent strength.

Methodology

Product prioritization

To highlight the drugs with the greatest potential for relevance in LMICs, we assigned a priority rating for each drug based upon a desk review of existing scientific literature and informal expert interviews. The priority rating reflects each drug's clinical potential and its potential for cost-effectiveness versus alternative products.

For example, if evidence indicates that a drug is clinically promising compared to alternatives, or if it has the potential to be cheaper than a clinically equivalent drug, we gave it a priority rating of "High". A drug with unclear benefit from a clinical and/or cost perspective was assigned a "Medium" rating, while a drug with no evidence of clinical or cost advantage was assigned "Low" priority. The priority rating does not incorporate patent strength, which we have assessed as a separate metric (*see next page*).

Note: What is promising for patients from a convenience, clinical or cost perspective is distinct from what constitutes therapeutic efficacy under the law. Nothing in this report should be construed as implying that clinical relevance of a drug would meet the efficacy test under patent law, which has its own set of requirements.

Patent strength

Whereas the priority rating indicates the need to expand patient access in LMICs, the strength of the patent should inform the strategies that are pursued to provide that access. For example, licensing may be the better strategy for drugs with strong underlying patents, while patent oppositions would be more appropriate for drugs with weak patents.

In order to assess patent strength, our team of lawyers and scientists first reviewed the patent landscape for each of the selected drugs. We determined through this process that secondary patents on these drugs were largely weak, and that patents for the base compounds of each drug fell into three basic categories:

- **Weak:** Considerable prior art, common knowledge, and/or data to challenge the patent for lack of inventive step and/or on the grounds of lacking efficacy
- **Questionable:** Prior art and data raise questions on inventiveness and/or efficacy, but further analysis of comparative data is required
- **Strong:** Little or no prior art suggesting the patent falls into the above categories, though further research is required

Patent strength detail (for lawyers)

In this report, the strength of a patent is based on whether a drug product meets legal requirements for inventiveness and/or therapeutic efficacy.

Inventiveness: In determining whether a drug is inventive by legal standards, we have adopted the standard approach of whether the invention claimed in a patent application would have been obvious to a person skilled in the field given the prior art available. Included in this assessment are practices that would be considered common general knowledge to a person in the art.

Efficacy: Here we employ the legal standard of the Indian Supreme Court, as set out in its recent April 1, 2013 decision in *Novartis AG v Union of India & Others*. We also focus on India because it is the home to the leading generic ARV producers.

The Novartis judgment has confirmed that for patents relating to medicines, the definition of efficacy will mean the ability of an invention to show enhanced therapeutic efficacy over an existing form of the subject matter in question. The court has confirmed that drugs claiming enhanced physico-chemical properties – such as stability, beneficial flow-properties and lower hygroscopicity – will not meet the therapeutic efficacy test.

For drugs claiming increased bioavailability, enhanced safety, and/or reduced toxicity versus existing forms, the Court has not stated conclusively whether these characteristics amount to enhancement of therapeutic efficacy.¹⁸ Such drugs must be assessed on a case by case basis, based on available data. We flag these open issues for each pipeline HIV drug in this report.

Executive Summary

Context

The ARV treatment pipeline includes many promising options in the short- and long-term. These options include new drugs and drug classes, dose reductions of existing drugs, as well as different approaches and delivery mechanisms (e.g. long-acting formulations).

In the next 5-10 years, the most promising technologies are drugs in existing ARV classes as well as a new class of drugs called **integrase inhibitors**. This drug class has near-term relevance for third-line therapy in LMICs, but eventually may be used in first-line as is the case in developed countries.

Though there is currently not a robust market for third-line ARVs in developing countries, this is not due to lack of need. Rather, it is due to the prohibitively high cost of current third-line options; limited access to viral load testing, which is needed to confidently diagnose treatment failure; and a relatively low proportion of patients requiring third-line given the still limited number on second-line.

However, as greater numbers of treatment-experienced patients develop resistance over time, the need for both viral load testing and third-line therapy is expected to increase. This has been the case in Brazil, which has one of the oldest patient cohorts on ARVs and is one of the only developing countries treating third-line patients in significant numbers. As countries in Africa and elsewhere prepare for a similar increase in both second- and third-line patients, it is critical for the global community to work toward ensuring affordable pricing, particularly given that current third-line options are cost-prohibitive for LMICs.

This report focuses on both existing and pipeline ARVs that have potential for relevance in resource-limited settings in the coming decade. We have assigned priority levels to these products to focus the global treatment community's attention on the products that are anticipated to provide the most benefit to patients globally versus existing options.

Summary Guidance

Our findings for the 11 drugs included in The Roadmap can be summarized as follows:

Tenofovir alafenamide fumarate (TAF) and **Darunavir (DRV)** are high priority drugs, both of which rest on weak or questionable patents and should be examined closely by parties working on patent opposition and patent law reform. **CMX157** and **Rilpivirine (RIL)** also have potential clinical relevance and should be subject to similar scrutiny. Examination of these patents and applications will also prove worthwhile to scholars wishing to evaluate the current workings of the pharmaceutical patent system, or as talking points for engaging with policymakers.

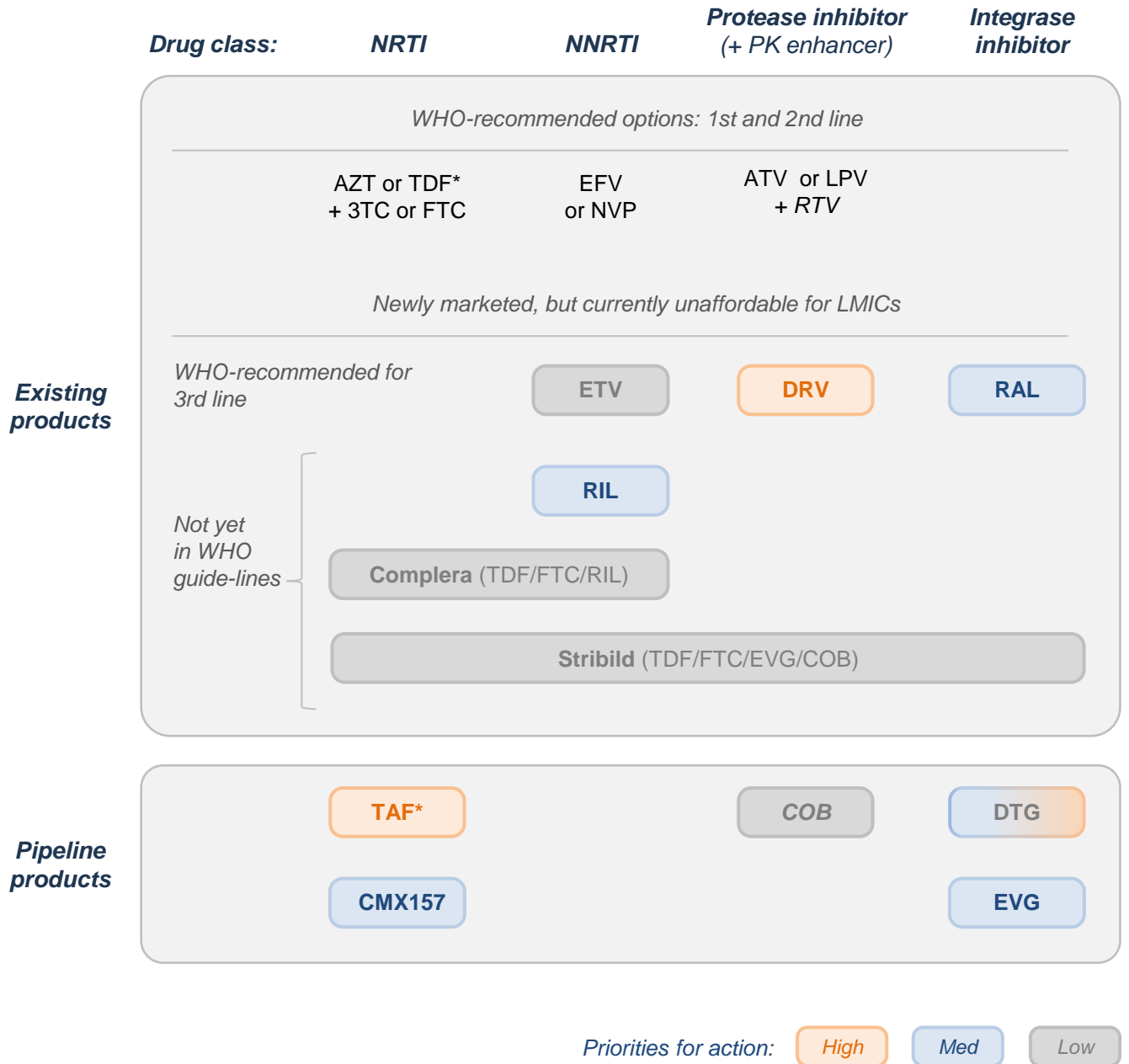
Dolutegravir (DTG) has med-high priority as the most promising integrase inhibitor in development from an efficacy standpoint, but for which drug interactions make its future LMIC-relevance unclear. Efforts to engage ViiV in expanding access (e.g. through VLs) should be prioritized amongst advocates given that it appears to be a strong patent. If patents exist on DTG in a country and access to affordable versions is not made available through generic VLs or access programs, CL work should be initiated immediately.

Elvitegravir (EVG) and **raltegravir (RAL)** are medium priority drugs which similarly appear to have strong patent claims, and for which advocacy to strengthen originator access programs can be pursued while further clinical data is generated. Additional research is encouraged in order to more fully understand the strengths or weaknesses of the underlying patents around these drugs.

Of the eleven focus drugs in this Roadmap, our present analysis indicates that **Cobicistat (COB)**, **Complera**, **Etravirine (ETR)**, and **Stribild** should currently be a lower priority for activists as compared to the other seven drugs previously mentioned. Pre-emptive work, including research on the patent strength and clinical relevance of these drugs, or patent challenges and VL efforts, should still continue, and monitoring the impact and potential of these drugs on HIV treatment remains vital nevertheless. Scholars may wish to focus on these four drugs when documenting a spectrum of secondary patenting practices.

In aggregate, our analysis demonstrates that a majority of base compounds for pipeline HIV drugs – 8 out of 11 – are not new chemical entities but rather modifications of existing compounds. Two of the drugs are merely new forms of tenofovir (TFV), an existing drug that is currently widely prescribed, and two are merely combinations of other drugs. This shines new light on how we understand secondary patenting and the need to shape policies accordingly.

Current ARV Landscape



*Nucleotide reverse transcriptase inhibitor (NtRTI)

Patent Quality Summary

Compound	Proprietor	Priority	Strength of base compound patent	Explanation
CMX157	Chimerix Pharmaceuticals/Merck	Medium	Weak	Prodrug of TFV
COB	Gilead Sciences	Low	Weak	Analog of RTV; no intrinsic efficacy of its own
Complera*	Gilead Sciences	Low	Weak	Combination, no more effective than individual drugs
DRV	Janssen Products (J&J)**	High	Questionable	PI similar to amprenavir and disclosed earlier
DTG	ViiV Healthcare and Shionogi	Med-High	Strong	Prior art exists against some claims, further research required
EVG	Gilead Sciences	Medium	Strong	Prior art exists but further research required
ETR	Janssen R&D (J&J)	Low	Questionable	Derivative of earlier known compounds
RAL	Merck	Medium	Strong	First integrase inhibitor
RIL	Janssen Products (J&J)	Medium	Weak	Disclosed in earlier patent for cancer
Stribild	Gilead Sciences	Low	Weak	Combination, no more effective than individual drugs
TAF	Gilead Sciences	High	Weak	Another prodrug of TFV, with a fumarate salt like TDF

*Patent quality assessment is for the patent application covering the combination of RIL, TDF and FTC. For Complera, the individual patents for RIL, TDF and FTC are also relevant.

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HIV/AIDS Roadmap

CMX157

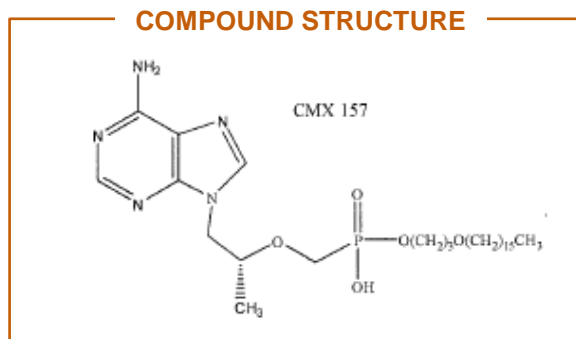
US brand name: N/A

PRIORITY: MEDIUM

Lags TAF in development; may become high priority if favored by clinical data

PATENT QUALITY: WEAK

- Proprietor: • Chimerix Pharmaceuticals
- Drug class: • Nucleoside reverse transcriptase inhibitor (NRTI)
- Status: • Promising Phase I results in 2008¹³, but progress stalled while Chimerix sought a financial backer.¹⁷
- Phase II now in process through Merck under an exclusive license.⁸
- Also under investigation for long-acting formulations.¹



- Relevance: • A prodrug of TFV and an alternative to TAF, an which is also in development (see page 36). CMX157 lags behind TAF in development, but comparative clinical data is not yet available and will need to be reviewed to determine CMX157's relevance.
- Has an improved pharmacokinetic profile to TDF and potential for a better toxicity profile given a lower dosage.¹
- Its low dosage and long half-life make long-acting formulations (e.g. once weekly or once monthly injections) a possibility.¹
- Patent considerations: • Exclusively licensed to Merck in July 2012 for development and commercialization.¹⁷
- Base patents expected to expire in 2029.

STRATEGIES FOR ACCESS

- The first strategy for CMX157 should be pre-grant patent oppositions, given the weak nature of the patents.
- If the patent is already granted in a given country, post-grant challenges should be filed alongside direct advocacy with the company for inclusion in its access program.
- Coordinated advocacy amongst actors in countries where the drug is patented could result in a VL, but this strategy should be used to complement the oppositions strategy.
- If this route fails, unless a government use or emergency CL provision is available and utilized, a general CL can be requested three years after the grant date of the patent. Given that the application for the base compound is still under examination in a number of countries, this option is unlikely to be available until 2015/16 at the earliest.

PATENT QUALITY ASSESSMENT

Summary

CMX157 is a lipid (1-O-hexadecyloxypropyl) conjugate prodrug of the acyclic nucleotide analog TFV. A number of publications disclosed CMX157 prior to the filings of the key patents claiming its structure and method of use. The prior art suggests that the patent applications claiming the base compound CMX157 lack inventive step. Regarding the efficacy test, early data shows that any improvements over the known forms are likely to be only pharmacological and not therapeutic.

Three key secondary patents were identified, covering methods of use and the salt, enantiomers, isomeric and racemic forms of CMX157. These patents all appear to lack inventive step in light of the prior art and do not meet the Indian efficacy test.

Main Compound Patents: WO 09/094190 and WO 09/094191

Is it inventive?

Two concurrently filed patent applications cover the base compound for CMX157. They both claim a series of esters of phosphorylated compounds and their method of use, and claim CMX157 in combination with other antiretroviral drugs.

However, at the time of filing these patents, the general structure and use of a number of the compounds relating to or covering CMX157 had already been disclosed in the public domain. For example, hexadecyloxypropyl tenofovir (same compound as CMX157) was disclosed in Antimicrobial Agents and Chemotherapy, 51(10), 3505 (2007) and other claimed compounds were similarly disclosed in WO 06/076015, US 2004/019232 and WO 06/110655. The prior art suggests that the patent applications claiming the base compound CMX157 lack inventive step.

With respect to claims covering CMX157 with other antiretroviral drugs, the existing prior art renders such combinations obvious as they highlight the claimed advantages of the general compounds relating to or covering CMX157. It would have been an obvious step to substitute CMX157 in any of the combination treatments.

Is there efficacy?

CMX157 should be considered a new form of the known compound TFV and its prodrug tenofovir disoproxil (TD). Until the final clinical trial data is released, the question of whether CMX157 can be considered to enhance the efficacy of previous known forms cannot be answered conclusively. However, early indicators can be used to assess whether CMX-157 would meet the current efficacy test.

The first consideration is that in the data provided in the patent applications, CMX157 is incorrectly compared against the parent compound (TFV). The applicant submitted that CMX157 is more potent than TFV (example 1 in the patent applications). However, a more meaningful and accurate comparison for the efficacy test would be against the known prodrug TD.

The second consideration is that after uptake into cells, CMX157 would remove and metabolize the prodrug back to the parent TFV. Therefore, the active species would still be the known form TFV. No scientific basis is provided in the current patent applications for why resistance profiles would differ if the active agent is identical.

Finally, current data shows CMX157 may have pharmacological advantages over TFV, though this is still speculative. For instance, CMX157 is understood to be more stable in blood plasma than TFV, which could lead to improved bioavailability. In addition, early indications show that CMX157 may be better tolerated than TD in patients and have lower kidney toxicity due to its lower dosing. However, because the optimal clinical dose has not yet been selected, the reduction in toxicity remains speculative. CMX157 is also speculated to bring the viral load down more rapidly because it is able to achieve higher intracellular levels of free TFV. However, for the purpose of the efficacy test, all these comparisons should be made against TD and not TFV.

In light of current data, it appears that all the benefits of CMX157 over the known forms of TFV and TD are pharmacological as opposed to therapeutic. Improved stability would not meet the therapeutic efficacy test. Bioavailability and tolerability are not conclusively considered improvements to therapeutic efficacy based on the recent Supreme Court decision in India. If this remains the case, then CMX157 may not be considered to enhance the efficacy of the known form. Further analysis will be needed as more data becomes available.

Secondary Patents: WO 11/053812 , WO 11/100698, and WO 11/139709

There are three additional applications of note:

WO 11/053812 claims the use of CMX157 in the treatment of viral infections and related pharmaceutical compositions. It is unclear how this application can be differentiated from the method of use claims covered by the primary applications discussed above. Thus the application should not be considered inventive.

WO 11/100698 covers salt forms, enantiomers, isomers and racemates of CMX157, as well as methods of their use. This application appears to lack any inventive step in light of the existing prior art and common knowledge for obtaining such forms. Regarding efficacy, the data submitted in the patent suggest that the forms presented show improvement only in stability (compared to the base compound disclosed in the earlier applications). Improved stability does not meet the standard of improved therapeutic efficacy.

WO 11/139709 claims a method for using CMX157 and its salt form by providing a schedule for daily to weekly dosing between 25-2000mg. The claims also cover use in combination with other HIV drugs and in relation to treating hepatitis B (for which TFV is also used). As with WO 11/053812, it is difficult to see how this application can be considered inventive over the methods of use in the earlier primary applications discussed above.

Cobicistat (COB)

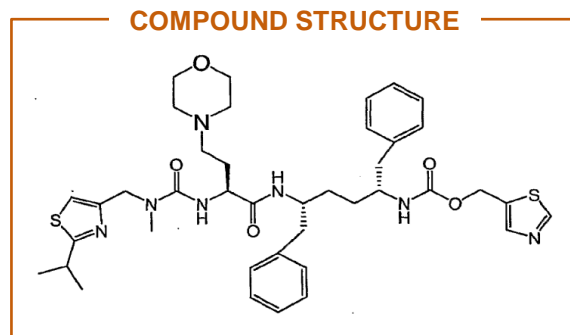
US brand name: N/A

PRIORITY: LOW

No demonstrated advantage to RTV

PATENT QUALITY: WEAK

- Proprietor: • Gilead Sciences
- Drug class: • Pharmacokinetic (PK) enhancer; boosts protease inhibitors (PIs) & EVG
- Status: • Phase III clinical trials; submitted to FDA as a separate compound in June 2012.³
• EMA Marketing Authorization Application approved May 2012.



- Relevance: • Has demonstrated non-inferiority but no clinical advantage to RTV when paired with atazanavir (ATV/r vs. ATV/COB). Side effect profiles of COB and RTV also appear similar.³
• Expected to be more costly to produce than RTV given the larger dosage (150mg of COB vs. 100mg of RTV daily when paired with ATV).
• Has no intrinsic efficacy of its own, hence will be marketed as part of a combination product only² (see page 34 for Stribild).
- Patent considerations: • Basic patent scheduled to expire in 2028.²
• Six generic manufacturers have been granted sublicenses under the MPP – Aurobindo, Emcure, Hetero, Laurus, Medchem, and Shasun – with royalty payments waived for pediatric formulations.¹⁶ Three additional generic companies – Matrix, Ranbaxy, and Strides – have been granted direct VLs from Gilead.¹⁵

STRATEGIES FOR ACCESS

- COB is not currently proven to be clinically superior or more cost-effective than RTV. In addition, the base compound patent for RTV expires between 2014 and 2016. As such we recommend activists and health and procurement agencies focus their energies on access to RTV.
- Since COB is a weak patent, oppositions should be filed, especially in countries with manufacturing capability and which were excluded from current VLs signed by Gilead.
- As COB has been licensed by Gilead Sciences to the MPP and generic producers in India, over 100 countries are covered and do not require direct advocacy for access.*
- Additional steps for addressing the numerous countries left out of the current VLs include:
 - 1) Advocate directly to Gilead and generics (and/or the MPP) to include the excluded countries within the licenses;
 - 2) Advocate directly to Gilead to include these countries within its access program or to offer price reductions;
 - 3) File for CLs in excluded countries, preferably through a coordinated global campaign, should the patents be granted;
 - 4) Employ government use or CL under emergency provisions to accelerate access.

*Generic companies that have direct licenses with Gilead were granted semi-exclusive rights to sell in additional countries, including Sri Lanka, Thailand, Botswana, Namibia, El Salvador, Ecuador, Indonesia, Kazakhstan and Turkmenistan. However, companies will be paying Gilead 15% royalties on sales to these countries.

PATENT QUALITY ASSESSMENT

Summary

COB is a close analog of RTV and structurally similar, but unlike RTV it has no intrinsic activity in combating HIV, acting only as a booster for other drug compounds. There are a number of earlier patents filed by Abbott Laboratories for RTV that could be used to challenge the inventiveness of COB, given the slight structural differences. In addition, although COB has been documented as “non-inferior” when compared to RTV in a number of clinical trials, there is no demonstrated superiority. Therefore, there is no evidence that COB offers any enhancement of efficacy over RTV in the boosting of other antiviral drug combinations.

Main Compound Patents: [WO 08/010921](#), [WO 08/103949](#), and [WO 09/008989](#)

Is it inventive?

COB is a close analog of RTV and retains the same core structure, differing only in two positions. RTV has intrinsic activity in combatting HIV through inhibition of the protease enzyme, as well as indirect activity to inhibit cytochrome P450 enzymes, preventing metabolism of other drugs and enhancing their effects. By comparison, COB has no intrinsic activity and acts only through inhibition of cytochrome P450.

Given the close structural similarities of COB and RTV and the fact that RTV was already known to inhibit cytochrome P450 (Abbott, US Patent 6703403), it is unsurprising that COB displays this activity. In addition, there are a number of earlier patents filed by Abbott protecting RTV which have broad claims that overlap or match the core compound structure of COB. With respect to the two structural positions that differ, the prior Abbott patents suggest the changes made by Gilead could, therefore, be considered obvious.

Gilead may argue that COB as compared to RTV improves the cytochrome P450 enzyme inhibition. However, this argument must be understood in light of the fact that COB has a higher dosage than RTV (150mg versus 100mg per day) when paired with ATV and other PIs. Gilead may also argue that COB prevents the development of drug resistance given that it lacks any intrinsic activity to combat HIV. However, there is no public data available to support this assertion, and it is based on an unlikely hypothetical assumption where a patient would take RTV without another HIV medication.

Is there efficacy?

Overall, there is no data that suggests an enhancement of efficacy for COB over RTV in the boosting of other antiviral drugs. In terms of cytochrome P450 inhibition, COB has been documented as being “non-inferior” to RTV in a number of clinical trials. Moreover, any comparisons of improvement must bear in mind the difference in dosage.

With respect to the claim that COB has a reduced side-effect profile over RTV, there is no evidence to date substantiating this. Indeed, it has been shown in studies of COB that renal toxicity may be a problem.

Gilead may also claim increased solubility of COB, which would make it easier to formulate into dosage forms relative to the insoluble RTV. However, in patent application WO 09/135179 (see page 34 for Stribild), Gilead concedes that a number of physicochemical properties of COB make it difficult to handle and process on a large scale (see page 1, line 17 onwards of WO 09/135179).

Darunavir (DRV)

US brand name: Prezista

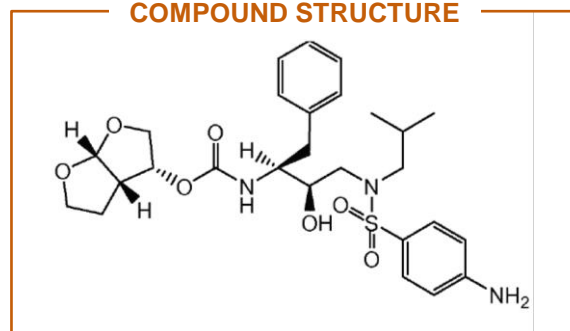
PRIORITY: HIGH

Preferred PI with potential to be price-competitive as volumes increase

PATENT QUALITY: QUESTIONABLE

- Proprietor: • Janssen Products (J&J)
- Drug class: • PI; requires boosting with a PK enhancer
- Status: • FDA approved for adults and children three years and older.
- Generic version from Hetero approved by the Global Fund ERP in May 2012, making it the first generic third-line product available for donor-funded procurement.²⁵

COMPOUND STRUCTURE



- Relevance: • Boosted DRV is WHO-recommended for third-line therapy in combination with RAL and ETR. However, DRV has potential relevance for second-line if it becomes price-competitive with current PIs (e.g. lopinavir (LPV)) as volumes grow.
- Sales remain small in developing countries given current pricing (\$730-1095 per patient per year²⁵) and low numbers of patients requiring third-line. In addition, there is currently no fixed-dose combination (FDC) product combining DRV with RTV, while FDCs do exist with RTV and the other two commercially available PIs (LPV and ATV).
 - Latest WHO treatment guidelines (2010) recommend a 600mg twice daily dosage, which will require updating given recent approvals in the US and Europe for an 800mg once daily tablet.
 - In the US, DRV and ATV are preferred PIs and used for treatment-naïve patients.²⁸
- Patent considerations: • The main compound patent expires in 2013², however various secondary patents have been filed for key intermediates, polymorphic forms, and combinations with other drugs (see next page).
- One secondary patent in the name of the US National Institute of Health (NIH) was licensed to the MPP in 2010. However, because Janssen holds other additional patents, which could potentially block generic production, this license is largely irrelevant.²⁵
 - Though Janssen/J&J does not plan to negotiate with the MPP²⁵, in November 2012 they announced that they would not to enforce patents in Sub-Saharan Africa and in Least-Developed Countries¹⁰, effectively opening the door for generic sales to these territories. However, approximately one fourth of patients needing ART live outside of these countries* and will still face barriers to generic access.
 - Janssen/J&J has also issued VLS to two generic companies – Aspen (South Africa) and Emcure (India) – though only for packaging and distribution of the drug in a limited geographic scope. The terms of these licenses are not public.²⁵

STRATEGIES FOR ACCESS

- DRV is high priority for activists given that it is available for use as third-line demand increases.
- Given that the base compound goes off patent in 2013 and was also not patented in India, patent oppositions against the secondary patents should be initiated immediately.
- If Janssen/J&J continue to display reluctance to issue VLS or expand their access program, advocates should coordinate a widespread CL campaign. Heightened importance should be placed on India as a key supplier country.

*Based on analysis of data from the World Health Organization (WHO)

PATENT QUALITY ASSESSMENT

Summary

DRV belongs to the PI class but requires co-administration with a PK booster such as RTV or COB (if approved). Earlier prior art exists which could be used to challenge the inventiveness of the patent application specifically claiming the base compound DRV. This includes an earlier international application that generally discloses DRV. DRV is structurally similar to the earlier compound amprenavir, which could also be potential prior art. As the base compound patent was not filed in India, we have not considered whether it would meet the efficacy standard.

Various secondary patent applications relating to DRV were identified, including combinations with other ARVs and a pseudopolymorphic form. There is considerable prior art to suggest that these secondary patents lack inventive step. From an efficacy standpoint, none of the secondary applications would likely meet the current requirements.

Main Compound Patent: WO 95/06030

Is it inventive?

WO 95/060303, filed in the name of Searle & Co/The Monsanto Company and licensed to Janssen, specifically claims the base compound DRV. Earlier prior art that may be relevant to inventiveness is the application WO 94/04492 in the name of the same parties, which claims a broad genus of compounds and generally discloses DRV. This earlier application could be considered to make the specific claim for DRV in WO 95/0606303 obvious. It is also noticeable that DRV is structurally similar to the earlier compound amprenavir, differing only in the terminal heterocycle. Further analysis is needed to assess the inventiveness of DRV in light of this prior art.

It is worth noting that this patent was never filed in India, being a pre-1995 patent.

Is there efficacy?

Given that this patent was not filed in India, we have not considered whether it would pass the efficacy test.

Secondary Patents: WO 03/049746, WO 06/005720, WO 03/106461, WO 99/67417, and WO 05/095410

Is it inventive?

A number of secondary patents have been filed by Janssen that are likely to be relevant to generic production.

WO 03/049746 claims DRV in combination with RTV. Given existing prior art, combining a PI like DRV with a PK enhancer would be obvious to a person skilled in the art. For example, WO 97/01349 by Abbott Laboratories already makes a claim for RTV to be used as a PK enhancer with other PIs. WO 99/67417 also claims the use of DRV with other PIs, RTV, indinavir and saquinavir.

WO 06/005720 claims a combination of TDF, RTV and DRV. There is a significant amount of prior art supporting this type of multiple therapy approach, including the use of PIs in combination with reverse transcriptase inhibitors. (See for example US Patent No. 5635523 by Abbott Laboratories.)

WO 03/106461 claims pseudopolymorphic forms of DRV. The pseudopolymorphs claimed are likely to lack inventive step because they are solvates/hydrates that inherently exist in the parent compound. Moreover, the techniques for obtaining pseudopolymorphs are known in the art and commonly used in industry. In this case, there is no problem solved by the development of pseudopolymorphs and no unexpected advantage offered by this formulation.*

Is there efficacy?

WO 03/049746 and WO 06/005720 would be considered new forms of known substances, given that they combine existing HIV compounds. Neither of these applications claim any therapeutic efficacy. The only benefit claimed is improvement of patient compliance and as such, under current requirements, would not meet the efficacy test.

WO 03/106461 would also be considered a new form of a known substance, given that DRV was disclosed in the earlier patent WO 95/060303. Based on publicly available data, the pseudopolymorphic forms claimed in this application do not demonstrate an increase in therapeutic efficacy over the darunavir base compound. While it is claimed the pseudopolymorphs possess improved stability and enhanced bioavailability, these assertions have not been proven to date in oppositions.*

Other relevant secondary patents of interest:

- WO 99/67417, held in the name of the US Government/ National Institutes of Health, is for an assay and method of use for treating HIV by combining DRV with other PIs such as RTV, indinavir and saquinavir. This patent forms the basis of a licensing agreement between the National Institutes of Health and the MPP. However, it is worth noting that the equivalent European application EP 1088098 is currently being opposed by Teva Pharmaceutical Industries on various grounds, including the lack of inventive step.
- WO 05/095410 in the name of Janssen covers the preparation of key intermediates for DRV. Further analysis is needed to establish whether this patent is inventive and/or relevant to generic producers.

**The pseudopolymorphic form of DRV (Indian Application No. 3598/DELNP/2004) has already been successfully opposed by pre-grant oppositions in India*

Dolutegravir (DTG)

US brand name: N/A

PRIORITY: MED-HIGH

Most promising integrase inhibitor in development

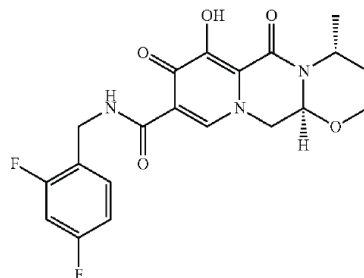
PATENT QUALITY: STRONG

- Proprietor: • ViiV Healthcare and Shionogi
- Drug class: • Integrase inhibitor
- Status: • Phase III trials with Expanded Access.*
- Under priority review by the US FDA (intended for products with potential for significant improvement versus alternatives); new drug application submitted in Dec 2012, which includes results from four pivotal trials.⁵

- Relevance: • Considered the most promising integrase inhibitor given a once-daily, low-milligram dosage; no requirement for boosting (unlike EVG); and potential for low-cost production in the absence of patent barriers.^{1,3} Demonstrated non-inferiority to RAL in treatment naïve patients and superiority in patients failing first-line therapy who have not yet been treated with an integrase inhibitor.⁶ Also demonstrated superiority to Atripla (TDF/FTC/EFV) when combined with abacavir (ABC) and lamivudine (3TC), driven largely by reduced side effects.²⁵
- Overcomes resistance to RAL with twice daily dosing, making it relevant for multi-drug resistant patients.⁴
 - Also has potential for treating HIV-2, which is resistant to RAL and EVG.¹
 - However, has known drug interactions with other ARVs and rifampin (a TB drug), which results in either increased or reduced drug exposure.²⁵ It is unclear how these issues will impact the drug's relevance in resource-limited settings.²⁵

- Patent considerations: • Basic patent expected to expire in 2026 with a patent application pending in India.²
- Patents for synthesis processes and intermediates expected to expire in 2029.²
 - No VLs currently exist or are expected, though consistent with their current access program, ViiV is expected to offer “access pricing” to LICs and negotiate prices for MICs on a case-by-case basis.^{3,25}

COMPOUND STRUCTURE



STRATEGIES FOR ACCESS

- Since DTG appears to be a stronger patent and a med-high priority drug, the first line of advocacy should be with ViiV and Shionogi for an inclusive access program.
- These efforts may be complemented through advocacy with the MPP to encourage ViiV/Shionogi to issue VLs so that DTG has the broadest possible reach across LMICs.
- If these companies display reluctance to expand their access programs or issue VLs, a coordinated CL campaign should be launched for MICs likely to be excluded from the access program.
- Prior art research should continue, and if a strong case can be built, patent oppositions should be filed against this drug. However at the present time we recommend that other advocacy strategies be employed first.

*Expanded access is a means by which manufacturers make investigational new drugs available, under certain circumstances, to treat a patient(s) with a serious disease or condition who cannot participate in a controlled clinical trial.

PATENT QUALITY ASSESSMENT

Summary

DTG falls within the class of integrase inhibitors and, unlike EVG, it does not require a booster. Structurally, DTG appears to differ from earlier integrase inhibitors, which suggests it may be inventive and also meet the efficacy test. However, preliminary searches have highlighted potential prior art, which requires further evaluation to assess the true strength of the patent and its efficacy.

A key secondary patent application for DTG relates to its prodrug. Substantial prior art exists around prodrug techniques, and as such this application appears to lack inventive step. With respect to efficacy, there is no data in the patent application to suggest that the prodrug improves oral delivery or the therapeutic efficacy of DTG.

Main Compound Patent: WO 06/116764 (Shionogi/SmithKline Beecham)

Is it inventive?

This patent application claims the compound by general structure. Structurally, DTG appears to differ from the earlier integrase inhibitors RAL and EVG. However, a very preliminary analysis has highlighted U.S. Patent Publication No. 2005/0054645 as being potential prior art that may question the inventiveness of the compounds claimed in this application, including DTG. Further detailed prior art searches will be required to assess the strength of the patent covering the base compound.

Is there efficacy?

For the purpose of deciding whether an opposition can be filed on this ground, further analysis of the prior art is necessary to establish whether DTG can be considered a new form of an existing substance that provides an enhancement of efficacy.

Secondary Patents: WO 10/011812 (Shionogi/GSK)

Is it inventive?

This patent application claims ester prodrugs, tautomeric forms (e.g. enantiomers and isomers) and salts of DTG. The esters are formed via the hydroxyl group on the tricyclic ring. A series of potential esters are disclosed but it is not known at this stage whether any are clinically relevant.

Prodrugs have been widely used in the antiretroviral field for a number of other compounds including TFV where disoproxil esters (TD), phosphoramidate (TAF), and lipids (CMX157) have all been used. The advantages offered by prodrugs are well known and this would appear to be an obvious approach for delivery of any new antiretroviral compound. Various prior art exists that could be used to challenge the inventiveness of this patent.

Similarly, obtaining tautomeric forms and salts of a compound is common general knowledge for which substantial prior art exists.

Is there efficacy?

The prodrug covered by the patent would be considered a new form of the known substance DTG (see WO 06/116764 above).

If an ester prodrug is chosen as the preferred form of DTG, further investigation would be required to establish whether this prodrug form has any enhancement of efficacy/clinical benefit over the base compound DTG. As filed, it does not include any data that could be used to demonstrate that the prodrug improves oral delivery of DTG. Therefore, this patent as filed is questionable in terms of meeting the efficacy standard.

Other Applications: WO 10/068262 and WO 10/068253

Other applications of interest relating to DTG include WO 10/068262 (intermediate compounds) and WO 10/068253 (synthesis process). Further analysis needs to be carried out to assess the strength of these patents.

It is possible that DTG, like EVG, could be used as part of a combination approach to combat HIV. As a result, additional patent applications could be filed. When details about the marketed product become available, a further search will be required.

Elvitegravir (EVG)

US brand name: N/A

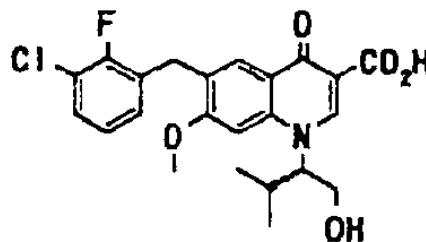
PRIORITY: MEDIUM

Clinical relevance to be determined, with potential to become high priority if favored to DTG

PATENT QUALITY: STRONG

- Proprietor: • Gilead Sciences
- Drug class: • Integrase inhibitor; requires boosting with a PK enhancer
- Status: • In Phase III clinical trials, with FDA submission in June 2012.
- EMA Marketing Authorization Application validated in June 2012.
 - Phase II study for children over 12 is in progress.²
- Relevance: • Demonstrated non-inferiority to RAL³, the only currently approved integrase inhibitor, though DTG (page 20) is currently considered the most promising pipeline integrase inhibitor.¹
- May still be relevant as part of Stribild (page 34) or as part of a similar fixed-dose combination which substitutes TAF (page 36) in place of TDF.
 - Also potential for generic suppliers to develop lower-cost fixed dose combinations that contain EVG.
- Patent considerations: • Patent protected through 2023.²
- Six generic manufacturers have been granted VLS through the MPP – Aurobindo, Hetero, Emcure, Laurus Labs, MedChem, and Shasun – with royalty payments waived for pediatric formulations.¹⁶ Three additional generic companies – Matrix, Ranbaxy, and Strides – have been granted direct VLS from Gilead.¹⁵

COMPOUND STRUCTURE



STRATEGIES FOR ACCESS

- As the clinical relevance of this drug is still in question, advocates may be better off waiting until further developments are announced.
- Since EVG has been licensed by Gilead Sciences to the MPP, approximately 100 countries are covered and do not require direct advocacy for access.
- Should EVG become important clinically, the next step would be to address the numerous countries excluded from the VLS. Here we have four potential strategies:
 - 1) In middle-income countries excluded from the Gilead licenses and where the patent has been granted, a coordinated CL campaign should be started in advance of when the requisite three years will have elapsed from the date of patent approval;
 - 2) Advocate directly to Gilead and generics (and/or the MPP) to include these excluded countries within the licenses;
 - 3) Advocate directly to Gilead to include these countries within its access program;
 - 4) Prior art research should continue, and if a strong case can be built, patent oppositions/revocation actions should be filed against this drug in excluded countries and in India as a supplier country.

PATENT QUALITY ASSESSMENT

Summary

EVG is an integrase inhibitor discovered by Japan Tobacco Inc. and exclusively licensed to Gilead Sciences.

The basic structure of EVG is based on the quinolone carboxylic acid structure found in the –floxacin family of antibacterials. However, from initial research, it appears a number of substitutions were made to EVG over the prior art to suggest it is inventive. From an efficacy standpoint, there do not appear to be similar compound structures disclosed in the prior art. Therefore, EVG is unlikely to be considered a new form of an earlier compound.

Key secondary patents relating to EVG include its crystal forms and methods of use. There is substantial prior art and common knowledge to show that obtaining new crystal forms is not inventive. In terms of efficacy, while the crystal forms claim improved stability, this assertion is not borne out from the data in the patent application. Also, improved stability does not equate to therapeutic efficacy under current standards.

With respect to the method of use patent application, in some countries such patents are not considered inventions and are unpatentable.

Main Compound Patent: WO 04/046115 (Japan Tobacco Inc.)

Is it inventive?

The basic structure of EVG is based on the quinolone carboxylic acid structure found in the -floxacin family of antibacterials (e.g. ciprofloxacin). While EVG is built using the basic compound structure found in the –floxacin family, various substitutions to groups were made at different positions in EVG to suggest it is inventive.* However, further research is required around the quinolone antibacterial compounds to identify whether some of the substitutions used for EVG had already been tried and what their effects were. Indeed, there are earlier quinolone carboxylic acids identified for use in relation to HIV and which have the same basic structure as EVG.

Note that for the equivalent patent granted in Europe, the main claims are in the form of use claims for treating HIV. Use claims may not be patentable in some countries (e.g. India) unless the claims are amended.

Is there efficacy?

Subject to further research, given the number of structural changes that were made to EVG over known compounds, it will likely be considered a new form. From this perspective, EVG should pass the requirement of the efficacy test.

**The stepwise development of EVG from the parent quinolone carboxylic acid is described in J. Med. Chem., 49(5), 1506 (2006).*

(It is worth noting, however, that in clinical trials EVG has only been used as part of a combination treatment with other antiretroviral compounds. As such, there is no clinical data on the individual efficacy of EVG and its intrinsic activity. Further review of data relating to EVG alone would be needed to determine this and what value the various substitutions to the EVG compound give over the known compounds.)

Secondary Patents: WO 05/113508 and WO 07/079260

WO 05/113508 covers crystal Forms II and III of EVG, which are claimed to be more stable. Given that crystalline forms inherently exist in the base compound and the techniques for obtaining them are common knowledge, there is significant prior art and grounds for arguing that this patent lacks inventive step. In India for example, a number of patent office decisions uphold this position.

With respect to the claim that the crystal forms are more stable, there is insufficient data in the patent specification to support this assertion. Furthermore, improved stability does not equate to improved therapeutic efficacy based on current interpretations in India.

WO 07/079260 is a method of use patent covering the use of RTV for improving the pharmaco-kinetics of EVG. In some countries, such as India, methods of use applications are not considered inventions and are unpatentable.

Etravirine (ETR)

US brand name: *Intence*

PRIORITY: LOW

Unlikely relevance given toxicity concerns

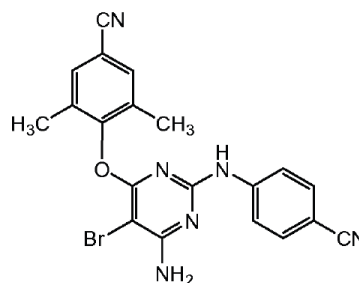
PATENT QUALITY: QUESTIONABLE

- Proprietor: • Janssen R&D (J&J)
- Drug class: • Non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Status: • FDA approved (Jan 2008) for adult patients who demonstrate resistance to other NNRTIs.²⁵
- Pediatric formulation FDA approved in March 2012.
 - WHO-recommended as a potential third-line drug, and for treatment experienced children above the age of six.

- Relevance: • First NNRTI to demonstrate antiviral activity in patients with an NNRTI-resistant virus.¹²
- However, significant toxicity concerns relating to severe skin and hypersensitivity reactions, including the potentially fatal Stevens-Johnson syndrome.¹³
 - RIL likely to be considered a better option in light of toxicity issues.
 - Currently priced at \$438 per patient per year.²⁵

- Patent considerations: • Basic patent is due to expire in 2019, but additional patent applications, if granted, may extend until 2026.^{2,25}
- There is currently no generic source for the product. Janssen/J&J have filed widespread patent applications in developing countries, and have announced their intention not to negotiate with the MPP.²⁵
 - Aspen holds a royalty-free, non-exclusive license to register, package and distribute (but not produce) the drug in sub-Saharan Africa.^{2,25}

COMPOUND STRUCTURE



STRATEGIES FOR ACCESS

- Since ETR is unlikely to be relevant for LMICs due to toxicity concerns, we recommend that advocates do not prioritize this drug.
- However, in anticipation that this situation may change, advocates may consider directing energies towards pressing Janssen to expanding its access program to include a larger number of LMICs, and/or to enter into access-friendly VLs. This broader advocacy with Janssen will support any efforts on ETR should the drug become clinically significant at a later stage.

PATENT QUALITY ASSESSMENT

Summary

ETR belongs to the group of NNRTIs. Various prior art exist which disclose structurally similar compounds that could be used to challenge the inventiveness of the patent application covering the base compound. Therefore, there may be scope to make an argument that ETR is a derivative compound and must, therefore, meet the efficacy test. Further analysis of comparative data would be required.

The secondary patent application covering a solid oral dosage formulation uses commonly known techniques, which should be considered obvious. In terms of efficacy, this application claims to provide improved solubility and bioavailability over the base compound. However, these claimed improvements alone may not meet the therapeutic efficacy requirement.

Main Compound Patent: WO 00/27825

Is it inventive?

The base compound for ETR is disclosed in Example B14 and in Table 2 as compound no. 26 in this patent application. Various items of prior art exist disclosing similar compound structures that could be used to build a case against the inventiveness of this patent. In particular, claim 1 of EP 0945442 encompasses compounds which differ only in not having the halo substitution in the pyrimidine ring. Further analysis of the prior art, in particular EP0945442, and any data comparing earlier similar compounds is necessary to establish the strength of an inventiveness argument.

Is there efficacy?

Given the similar compound structures described in the prior art and their activity, there is potential to argue that ETR is a derivative compound and, therefore, a new form of a known substance(s). As such, the base compound must satisfy the efficacy criteria over the known forms described in the prior art. Further analysis of comparative data would be needed to develop these arguments.

Secondary Patents: WO 01/22938

Is it inventive?

Patent application WO 01/23938 claims a solid oral dosage formulation. ETR is practically insoluble in water across a range of pH values and requires a dispersion aid or “excipient.” The product monograph for ETR discloses that hypromellose (hydroxypropylmethylcellulose-HPMC) is an excipient in the product as marketed. The use of HPMC as a dispersion aid for insoluble compounds was well known in the art for similarly insoluble compounds (including within the HIV field) and would be obvious to a person skilled in formulation techniques.

Is there efficacy?

The solid dispersion of ETR is a method of formulation for a poorly soluble drug substance. As such it is simply a method to ensure adequate bioavailability of ETR when given orally. Based on current legal precedent, improved solubility and bioavailability alone may not meet the current standards for efficacy.

Raltegravir (RAL)

US brand name: *Isentress*

PRIORITY: MEDIUM

Likely to be inferior to DTG, but may still be relevant for HIV/TB co-infection

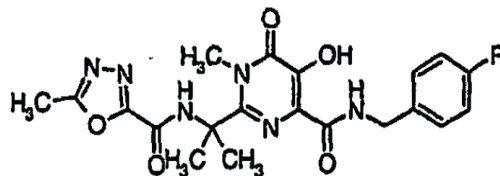
PATENT QUALITY: STRONG

- Proprietor: • Merck
- Drug class: • Integrase inhibitor
- Status: • FDA-approved for adults (Oct 2007) and children aged two to 18 years and weighing at least 10kg (Nov 2011).
- Listed in WHO guidelines as a potential third line therapy for adults & adolescents along with boosted DRV and ETR.

- Relevance: • First and only integrase inhibitor approved by a stringent regulator (*not including EVG, which has been approved only as a component of Stribild*).
- Pipeline integrase inhibitor DTG has demonstrated greater efficacy than RAL²¹, and is expected to have a lower dosage and better resistance profile; however, due to DTG's expected interaction with rifampin, RAL may remain a relevant option for patients co-infected with tuberculosis.
 - Outside of developed markets, patient numbers remain low except for Brazil, which has ~6,000 patients on RAL.²⁵
 - Current branded price is \$675 per year for low-income and all Sub-Saharan African countries.²⁵

- Patent considerations: • The basic patent, which has been granted in India, is due to expire in 2023. A patent application on the compound's potassium salt could potentially extend it to 2027 if granted.²⁵
- VLs were signed with two generic suppliers in India – Matrix (Mylan) and Emcure – but generic versions have yet to become available.^{25,26}
 - A technology transfer agreement with the Government of Brazil is underway, which could reduce the price from >\$5,800 per patient per year (2010 price) to \$4,000 ppy in 2015.²⁵

COMPOUND STRUCTURE



STRATEGIES FOR ACCESS

- Since RAL appears to be a stronger patent and a medium priority drug, the first line of advocacy should be with Merck for an inclusive access program.
- There are two VLs in place with Indian generic companies. Advocates may wish to check with the generic companies to understand when the product will come to market.
- If these companies display reluctance to expand their access programs or issue VLs, a coordinated CL campaign should be launched for MICs likely to be excluded from the access program.
- Prior art research should continue, and if a strong case can be built, patent oppositions should be filed against this drug. However at the present time we recommend that other advocacy strategies be employed first. Secondary patents can of course be opposed at any time.

PATENT QUALITY ASSESSMENT

Summary

RAL is an integrase inhibitor and the first compound in this class to be developed to marketing. Based on a preliminary assessment, there does not appear to any prior art that could question the inventiveness of the base compound patent application. Therefore, RAL appears to be a new compound and would not be subject to the efficacy test.

Secondary patent applications of note claim the potassium salt of RAL. There is considerable earlier common knowledge and prior art that could be used to challenge the inventiveness of these patents. Given that salt forms can only ever improve the pharmacokinetics of a base compound, such improvements would not meet the current standard of therapeutic efficacy.

Main Compound Patent: WO 03/035077

Is it inventive?

This international patent application claims the base compound for RAL (see Table 2, compound no 24). At the time of writing and based only on a preliminary search, there does not appear to be any prior art that is directly relevant for questioning the inventiveness of the compound. However, further extensive searches may reveal prior art that has not been considered for this version of the report.

Is there efficacy?

Based on the preliminary prior searches conducted for this report, it appears that there are no earlier known compounds that would cause RAL to be considered a new form of a known substance. Therefore, at the time of writing, the efficacy test does not appear to be applicable.

Secondary Patents: WO 06/060712 and WO 06/060730

International patent applications WO 06/060712 and WO 06/060730 relate to the end formulation of the marketed product Isentress, which employs the potassium salt. The claims of the applications include the potassium salt of RAL, including an anhydrous crystalline form. However the patent specifications provide no comparative data as to whether the anhydrous form has more advantageous properties than the basic potassium salt form.

There is considerable earlier common knowledge and prior art that could be used to challenge the inventiveness of these patents. For example, the basic compound patent application mentioned above describes the routine selection of salt forms including alkali metal salts such as potassium (see page 62, line 13 onwards). Moreover, as potassium salts are extensively used in the pharmaceutical industry, they would have been amongst the first salts of RAL to be prepared and tested.

Is there efficacy?

The potassium salt forms of RAL would be considered new forms of the base compound as disclosed in the earlier patent WO 03/035077. Given that salt forms can only improve the pharmacokinetics of a base compound - e.g. stability, solubility and bioavailability -- such enhancements alone may not meet the current efficacy standards. It is also worth noting that there is no data in the patent applications indicating how the salt form (in particular the anhydrous crystalline form) improves the pharmacokinetics of the free base compound.

Rilpivirine (RIL) & Complera

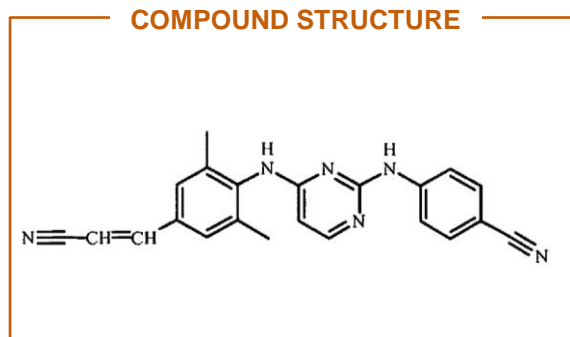
US brand name: Edurant (RIL), Complera (TDF/FTC/RIL)

PRIORITY: MEDIUM (RIL), LOW (Complera)

Complexities of use at approved dose need to be overcome

PATENT QUALITY: WEAK

- Proprietor: • Janssen Products (J&J)
(Gilead Sciences for TDF & FTC)
- Drug class: • NNRTI
- Status: • FDA approved for treatment-naïve adults in May 2011 (RIL) and Aug 2011 (Complera).
• Neither product currently included in WHO Guidelines.



- Relevance: • Offers significant advantages to EFV, including lower rate of adverse events^{2,4,23} and potential for lower pricing (*MSF reports generic production cost could be as low as ~\$10 per patient per year*).²⁴
• However, RIL is less effective than EFV in patients with high viral loads and presents a greater risk of virological failure.^{2,4,23} This poses a significant challenge given extremely limited access to viral load testing in resource-limited settings.
• Contraindicated with tuberculosis drugs rifampicin and rifabutin, creating a further challenge for LMIC given high rates of HIV/TB co-infection.²¹
• A long-acting, injectable form of RIL is currently in Phase I trials.^{3,8}
• Complera – the combination of RIL with TDF and FTC – is the second complete regimen in a single pill to be approved for first-line ART and will compete directly with Atripla (TDF/FTC/EFV) and Stribild (TDF/FTC/EVG/COB) in developed markets. However, even if obstacles associated with RIL are overcome in developing countries, the ideal fixed-dose combination product would be with TDF and 3TC (rather than FTC) for cost reasons.
- Patent considerations: • Basic patent for RIL set to expire in 2023. Patents for the combination with other drugs are under application.^{2,24}
• VL agreements are in place with four Indian generic manufacturers – Hetero, Emcure, Matrix, and Strides – plus Aspen of South Africa, and cover 112 countries.⁹

STRATEGIES FOR ACCESS

Rilpivirine

- Advocacy efforts are not high priority for RIL -- clinical improvements are needed first.
- Since existing VLs exclude many MICs, if advocacy is undertaken, emphasis should be placed on coordinating advocacy to J&J to expand VLs and/or access programs.
- The VL strategy should be co-ordinated with oppositions in key excluded MICs given that there are good grounds for opposing the base compound patent(s). This strategy would also complement oppositions against Complera.
- Simultaneous efforts should be made to issue CLs in excluded countries.

Complera

- Overall, this is not a high priority for advocates at the current time (see explanation above).
- Patent oppositions are the first strategy to go after Complera, given the weak nature of the patent (see also strategy for RIL). Activists have done a great job showing the public why combination products should not be granted patents unless they result in therapeutic benefit.
- If the patent is granted in a given country, another step can be to directly advocate with the company for inclusion in its access program.
- Coordinated advocacy amongst actors in countries where the drug is patented could result in a VL. Since TDF and FTC are already in the MPP licenses, advocates may pressure J&J to put RIL into the MPP as well. Advocates may also consider as part of this coordinated strategy to advocate to Gilead to expand its licensed territories.
- If the VL route fails, a CL can be issued three years after the patent is granted.
- Government use or a CL under emergency provisions, depending on local law, could be used as an accelerated option.

PATENT QUALITY ASSESSMENT

Summary

For the two patent applications that are relevant for the base compound RIL, there is a body of prior art that could be used to question their inventiveness. For the later of the two applications (which specifically claims the compound RIL), it could be argued that RIL is a derivative of ETR and, therefore, it should have to show efficacy over this known form. However, further analysis of comparative data would be needed to develop these arguments. For the earlier application, which discloses compounds generally covering RIL but for use with cancer treatment, it might be possible to raise the argument that as derivatives of ETR the compounds amount to a new use of a known form.

Three secondary patents of note were identified covering combinations and salt forms of RIL. There is ample prior art and general common knowledge in the field to challenge these secondary patents as being obvious. From an efficacy standpoint, none of the improvements claimed in these secondary patents would meet the current therapeutic efficacy requirement.

Main Compound Patent: WO 01/64656 and WO 03/016306

Is it inventive?

Published patent application WO 01/64656 filed in the name of AstraZeneca discloses a broad genus of compounds and claims RIL in a general manner. The compounds are described as inhibitors of cyclin-dependent kinases for use in the treatment of various cancers. However, it is not clear whether this patent application can be considered to provide protection for the base compound RIL outside of anti-cancer uses. US Patent 6838464 -- which stemmed from the international application WO 01/64656 -- is listed in the US FDA Orange Book against both the Edurant (RIL) and Complera products, suggesting that the base

compound RIL is covered without a specific limitation to cancer treatment. However, the interpretation of the scope of the claims filed in WO 01/64656 may differ country to country, with a possible argument that as the patent description only states the utility of the compounds for the treatment of cancers, the actual claims cannot therefore be extended to use for HIV.

Assuming for illustration purposes that WO 01/64656 does provide protection for the base compound RIL, it is notable that the compound structure disclosed is related to ETR, as both are based around a substituted pyrimidine molecule. The patent disclosing ETR (WO 00/27825 - see analysis on page 27) -- and related patents EP 0834507, EP 0945442 and EP 0945443 in the name of Janssen -- all disclose similar compounds. In particular, EP 0945443 discloses compounds very closely related to the general disclosure of RIL in WO 01/64656. As such, there is scope to raise an argument that the compounds and general disclosure of RIL in WO 01/64656 lack inventive step. However, because of the possible different uses of the compounds described in the prior art, the interpretation of inventive step may depend on the strictness of local patent laws vis-à-vis new uses of known compounds.

WO 03/016306 filed in the name of Janssen claims a broad genus of compounds including RIL specifically for use in the treatment of HIV. Given the general disclosure of RIL in the earlier application WO 01/64656, there is scope to argue that the specific claim for the RIL compound would have been obvious (depending on the strictness of local patent laws relating to new uses of known compounds). This earlier patent alongside those noted above relating to ETR would provide reasonable grounds for questioning the inventiveness of the specific claims for RIL made in WO 03/016306.

Is there efficacy?

In relation to application WO 03/016306, given the similar compound structures described in the prior art (in particular EP 0945443) and their activity, there is scope to argue that RIL is a derivative compound and therefore a new form of a known substance(s). As such, the base compound patent specifically disclosed in patent application WO 03/016306 needs to satisfy the efficacy criteria over the known forms described in the prior art. Further analysis of comparative data would be needed to develop these arguments.

It is also worth noting that where countries have a specific practice or provision for refusing new/second use patents (i.e. section 3d India), it would be possible to argue that the compounds claimed in WO 03/016306 are a new use of the general disclosure of RIL as set out in the earlier patent WO 01/64656.

With respect to application WO 01/64656, given that the claims of the compound relate to use for anti-cancer treatment, it would not be possible to apply an efficacy test as compared to the earlier prior art discussed above disclosing similar structured compounds. However, depending on the relevant country's law and practice, it might be possible to argue that the compounds claimed in WO/01 06456 are a new use of known substances, i.e. derivatives of the structurally similar compounds disclosed in prior art.

Secondary Patents: WO 05/021001, WO 06/024668, and WO 06/024667

There are three secondary patent applications filed by Janssen that are also important for the protection of the marketed products.

The first of these is the combination drug of RIL/TDF/FTC known as Complera, filed under application number WO 05/021001. There is a significant amount of prior art supporting this multiple therapy approach to HIV treatment, in particular the Atripla therapy where FTC and TDF are combined with another NNTRI, EFV. The substitution of one NNRTI (EFV) for another (RIL) would seem an obvious step. With respect to patents relating to FTC and TDF, since this report is concerned with the next generation of products, these drugs are not discussed here.*

The second patent application of note is WO 06/024668, containing claims to the hydrochloride salt of RIL and their polymorphic forms. Given the significant general common knowledge and prior art around salt selection and for crystalline forms of salts (including for NNRTIs and the use of hydrochloride salts), the claimed invention in WO 06/024668 would likely have been obvious to a person skilled in the area of formulations.

The other application of note, although not currently relevant to the formulated product as marketed, is WO 06/024667. This patent application contains claims to the fumarate salt of RIL and may be a defensive patent against a competitor using a different salt for formulation purposes. As for the patent claiming the hydrochloride salt, given the significant prior common knowledge and art around salt selection as described above, the claimed invention in WO 06/024667 would likely have been obvious to a person skilled in the area of formulations.

Is there efficacy?

The invention claimed in WO 05/021001 is a combination of previously known drugs and would, therefore, be considered a new form of a known substance. While the invention claimed in WO 05/021001 claims the benefit of reduced pill burden and increased patient compliance, neither of these demonstrates an enhancement of therapeutic efficacy.

The salt forms claimed in patent applications WO 06/024667 and WO 06/024668 would be considered new forms of the known substances disclosed in WO 01/64656 and WO 03/016306 (and arguably the earlier prior art patents discussed above, e.g. EP 0945443). As such, these applications would have to show an enhancement of efficacy over the known forms. Both applications claim improved stability and bioavailability, but under current legal precedent these factors alone may not equate to therapeutic efficacy.

*See however <http://www.i-mak.org/tenofovir/> for patent oppositions and analysis against patents for TD and TDF in India.

Stribild (TDF/FTC/EVG/COB)

US brand name: Stribild (formerly the “Quad Pill”)

PRIORITY: LOW

No clinical advantage demonstrated to lower-cost regimens

PATENT QUALITY: WEAK

- Proprietor: • Gilead Sciences
- Drug class: • Multiclass FDC consisting of TDF, FTC, EVG, and COB
- Status: • FDA-approved in Aug 2012 for treatment-naïve adult patients.
• Not currently listed in WHO guidelines.
- Relevance: • First integrase inhibitor-based FDC to enter the HIV drug market.
• Demonstrated non-inferiority to Atripla (TDF/FTC/EFV)³ and expected to capture a large share of the US market.¹¹
• However, appears unlikely to gain relevance in LMICs as there is no clear clinical advantage and will likely cost twice as much as generic versions of TDF/3TC/EFV. Furthermore, if integrase inhibitors are adopted in first-line treatment in LMICs, DTG appears likely to be the more preferred option from a clinical standpoint.¹
• Generic suppliers could also develop lower-cost alternatives to Stribild, e.g. substituting 3TC for FTC, or RTV for COB.
- Patent considerations: • Patents on constituent compounds extend as far as 2028.²
• Through the MPP, six generic manufacturers have been granted licenses to manufacture the combination drug and its constituent compounds, including Aurobindo, Emcure, Hetero, Laurus, MedChem, and Shasun.¹⁶ Three additional generic companies – Matrix, Ranbaxy, and Strides – have been granted direct VLs from Gilead.¹⁵

STRATEGIES FOR ACCESS

- This drug is low priority for LMIC advocates given that it is not cost effective versus alternatives.
- Patent oppositions may be filed on this combination drug if it does become relevant, given the weak quality of the patent. Activists have done a great job showing why combination patents should not be granted unless they result in a therapeutic benefit, and should continue to build on this. This drug in particular already has seen public comment by advocates around the high pricing by Gilead so efforts can be coordinated. (However, see also strategies for EVG and COB, as advocates will need to address patents on individual compounds in addition to the combination drug patent)
- If the patent is granted in a given country, one can directly advocate with Gilead for inclusion in its access program.
- Since Quad/Stribild has been licensed by Gilead Sciences to the MPP, approximately 100 countries are covered and do not require direct advocacy for access.
- The next step is to address the numerous countries excluded from the VLs. Here we have four potential strategies:
 - 1) Advocate directly to Gilead and generics (and/or the MPP) to include these excluded countries within the licenses;
 - 2) Advocate directly to Gilead to include these countries within its access program;
 - 3) File for CLs in excluded countries, preferably through a global CL campaign;
 - 4) Employ government use or CL under emergency provisions to accelerate access.

PATENT QUALITY ASSESSMENT

Summary

Two key secondary patents were identified claiming a bilayer tablet formulation and a solid carrier combining the four active ingredients EVG, COB, FTC, and TDF. Both applications lack inventive step given the significant prior art that exists for such formulation techniques. Regarding the efficacy test, as there is no therapeutic efficacy to the combination product that does not exist with its individual components, these combination patent applications would not be considered inventions.

It is worth noting that Gilead could switch the TDF component of this combination for its new TFV prodrug, TAF, should it be approved. For analysis of the patents relating to TAF, see page 37.

Secondary Patents: WO 10/091197 and WO 09/135179

Is it inventive?

There are a number of patents pertaining to the individual components, EVG, COB, FTC, and TDF that need to be considered in parallel to the patents discussed below. Analysis of the patents covering COB and EVG are discussed individually on pages 16 and 24. As this report is concerned with the next generation of products, FTC and TDF patents are not discussed here.*

Patent application WO 10/091197 relates to a bilayer tablet formulation in which the EVG and COB components are in one layer and the FTC and TDF components are in another. Bilayer tablets are, however, very common within the pharmaceutical industry and are a simple and obvious solution where incompatible materials are formulated into a single convenient dosage form. For example, diclofenac and misoprostol tablets (Artrotec) are formulated to keep the acidic diclofenac component separate from the acid sensitive misoprostol component. There are many additional examples of such formulations. As such, there is significant prior art to question the inventiveness of this patent application.

Patent application WO 09/135179 also attempts to claim the formulation of COB using a solid carrier on which the drug is either bound on the surface or in the pores of such a carrier. Later claims (claim 32) within the application expand this to include the other active components of the Stribild product. However, the use of carrier materials would be seen as the norm in terms of manufacture, so it is difficult to see any inventive step.

Is there efficacy?

The combination of these HIV drugs represents a new form of known substances. There is no therapeutic efficacy to the combination product that does not exist with its individual components. The application claims acceptable stability, and displays improved pharmacokinetic data, neither of which represents therapeutic efficacy. The application further claims that “the active compounds do not exert a negative impact on each other,” but again this cannot be taken as therapeutic efficacy. Gilead will also likely claim reduced pill burden and increased patient compliance, but neither of these represents enhancement of therapeutic efficacy.

*See however <http://www.i-mak.org/tenofovir/> for patent oppositions and analysis against patents for TD and TDF in India.

Tenofovir Alafenamide Fumarate (TAF)

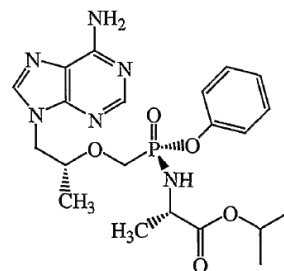
PRIORITY: HIGH

Potential to be cheaper & less toxic than TDF

PATENT QUALITY: WEAK

- Proprietor: • Gilead Sciences
- Drug class: • Nucleotide reverse transcriptase inhibitor (NtRTI)
- Status: • In Phase III clinical trials.
- Only being studied as a part of four-drug FDCs with FTC, COB, and either EVG or DRV.²⁷

COMPOUND STRUCTURE



- Relevance: • TAF is a prodrug of TFV with higher potency at less than one tenth the dosage. Selection of a 25mg dose has been reported, though interactions with COB – which boost TAF – support a 10mg dose for co-formulations.⁴
- When combined with FTC, EVG, and COB, TAF has demonstrated comparable efficacy to TDF but with an improvement in renal and bone safety profiles.²⁹ Given the much lower milligram dosage, TAF has the potential to provide benefits over TDF in terms of both toxicity and price.^{4,22}
 - However, it is unlikely to advance quickly as an option for LMICs unless fast-track approval is sought for the drug as a standalone, and not just as a component in FDCs.
- Patent considerations: • A patent application has been filed (*see next page*) which, if granted, would expire in 2021.²⁰
- Gilead has negotiated VLs with the MPP for its other pipeline ARVs (COB, EVG, and Stribild)¹⁶, but has yet to do so for TAF.

STRATEGIES FOR ACCESS

Given the potential of TAF to be more cost-effective and less toxic than TDF, advocates may wish to consider the following pre-emptive strategies:

- The first line of attack for TAF should be pre-grant patent oppositions, given the very weak nature of the patent.
- Advocates may also wish to use TAF in advocacy with governments around secondary patenting, as part of a broader strategy for access.
- If the patent is granted in a given country, the next step can be direct advocacy with Gilead for inclusion in its access program. Post-grant patent challenges may also be filed in that country.
- Where patents are granted advocates may also work to ensure the MPP is seeking VLs from Gilead.
- Otherwise if this route fails, a CL can be issued after three years.
- Government use or a CL under emergency provisions, depending on local law, could be used as an accelerated option.

PATENT QUALITY ASSESSMENT

Summary

TAF, formerly known as GS-7340, is not a new compound. It is another prodrug of TFV, but using a different ester as compared to the earlier known form TD. Given the existing prior knowledge for formulating antiviral compounds as prodrugs to allow intracellular absorption, substituting the disoproxil ester of TFV with an aryl phosphoramidate ester would have been obvious. The application also claims the fumarate salt of the ester prodrug, the same salt as used TDF. The use of fumarate salt for formulation purposes would be obvious in light of TDF and the other considerable prior art on salt selection for antiviral compounds.

From an efficacy standpoint, as TAF is a prodrug and also claims the fumarate salt of TFV, it will be metabolised in the body to its active monophosphate form. As a result, the active species will be exactly the same as that generated from TDF. By current standards TAF would not likely meet the efficacy standard.

Main Compound Patent: WO 02/008241

Is it inventive?

TAF is another prodrug of the NtRTI TFV. The patent application also claims the fumarate salt of the ester prodrug, the same salt as used in TDF and adefovir.

The earlier prodrug of TFV, TD, was prepared using a bis (isopropylloxycarbonyloxymethyl) ester to ensure adequate bioavailability. TAF adopts an identical approach, but instead uses an aryl phosphoramidate prodrug of TFV to increase activity. The use of a phosphoramidate group to increase activity of antiviral compounds has already been shown for a number of nucleosides, such as zidovudine (AZT) and stavudine (D4T), and would be considered obvious to try for TAF. The application also claims a fumarate salt for formulation purposes, as was adopted for TDF.

Given the existing prior knowledge for formulating antiviral compounds as prodrugs to allow intracellular absorption, substituting the disoproxil ester of TFV with an aryl phosphoramidate ester would have been obvious. Similarly, the use of fumarate salt for formulation purposes would be obvious in light of TDF and the other considerable prior art on salt selections.

It is worth noting that during prosecution of the European patent application, Gilead argued that the patentability of TAF resides in the choice of a single enantiomer, which possesses increased potency and reduced side-effects over the racemic form of the compound. However, identifying chirality (i.e. the differences between enantiomers and their activity) would be expected in racemic compounds like TAF, as it is common practice within the industry and part of routine testing to satisfy the requirements of regulatory bodies such as the US FDA.

Is there efficacy?

In 2004, it was reported that Gilead stopped development of TAF as it showed no clinical benefit over existing treatments. Given that TAF (and its fumarate salt) is a prodrug of TFV and will be metabolised in the body to its active monophosphate form, the active species will be exactly the same as that generated from TDF. As such, by current efficacy standards in India, TAF would likely not meet the efficacy standard.

To counter the efficacy requirements, Gilead will likely argue that TAF enables a higher intracellular delivery of TFV with less drug intake, thereby making it more cost-effective. However, as the prodrug metabolises back to TFV, there is no difference in the therapeutic efficacy between TAF and the earlier known forms of TD and TDF. Furthermore, improving cost-effectiveness does not equate to therapeutic efficacy.

Gilead may also claim there is a difference in toxicity between TDF and TAF. However, as patients would take a lower dosage of TAF, there will likely be decreased side effects. Moreover, reducing the amount of the drug to be taken (and thereby any toxicity) does not meet the current legal requirements for efficacy.

Secondary Patents: WO 04/064845 and WO 04/064846

It is not currently clear what the final set of patents will be around TAF, as Gilead is likely to file further patent applications on the final formulation. Ongoing review is required of the patent landscape.

However, two patents of relevance, WO 04/064845 and WO 04/064846, cover methods and compositions comprising TAF and FTC. Given the existing prior art, these combination patents are likely to be considered to lack inventive step and efficacy.

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