Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	darunavir/cobicistat (Prezcobix)
Indication	Used in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in treatment- naive and in treatment-experienced patients without darunavir (DRV) resistance-associated mutations (RAMS)
Listing request	As per indication
Manufacturer	Janssen Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in infectious diseases who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ART	antiretroviral therapy
CDR	CADTH Common Drug Review
HHS	(US Department of) Health and Human Services
DRV	darunavir
FDC	fixed-dose combination
RAM	resistance-associated mutation
PI	protease inhibitor

SUMMARY

1. BACKGROUND

Darunavir (DRV)/cobicistat 800 mg/150 mg (Prezcobix) is a fixed-dose combination (FDC) protease inhibitor (PI). In combination with other antiretroviral therapies, darunavir/cobicistat is indicated for the treatment of HIV infection in treatment-naive and treatment-experienced patients without DRV resistance-associated mutations (RAMs).[1] Darunavir/cobicistat is available in an 800 mg/150 mg film-coated tablet at a recommended dose of one tablet daily. The manufacturer submitted a price of $23.17 per 800 mg/150 mg tablet.

1.1 Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis. The analysis considered the daily drug costs of the darunavir/cobicistat (800 mg/150 mg) FDC compared with the cost of the individual drugs (darunavir [800 mg] boosted with ritonavir [100 mg]). The manufacturer's assumption of similar efficacy for the darunavir/cobicistat FDC versus darunavir boosted with ritonavir was based on a manufacturer-submitted naive indirect comparison (i.e., comparison of the results from single groups from different trials)[2] based on data from a phase 3 single-group open-label study (GS-US-216-0130)[3] and two registration studies (ODIN and ARTEMIS).[2] From this analysis, the manufacturer concluded non-inferiority in overall response, defined as patients achieving an HIV-1 ribonucleic acid (RNA) of less than 50 copies/mL for both the darunavir/cobicistat FDC and darunavir boosted with ritonavir. The unit drug prices for all comparators were obtained from the Ontario Drug Benefit,[4] except for the prices for maraviroc and zidovudine which were obtained from the Régie de l'assurance maladie du Québec Liste de médicaments.[5] All prices excluded markup and dispensing fees. The manufacturer considered drug costs only, omitting any costs associated with adverse events or drug administration or monitoring, as the drugs were assumed to be equivalent.

In the base-case analysis, the manufacturer indicated that the cost of the darunavir/cobicistat FDC ($23.17 daily) was equivalent to darunavir boosted with ritonavir.

In addition, the manufacturer compared the cost of the darunavir/cobicistat FDC with other antiretroviral therapy (ART) regimens. These regimens were based on the "preferred," "alternative," and "other regimens" (regimens that may be selected for some patients but are less satisfactory than preferred and alternative regimens) outlined in the US Department of Health and Human Services (HHS) guidelines on the use of antiretroviral drugs in HIV-1–infected adults and adolescents (February 2013).[6] In the 2013 guidelines, the following were listed under "preferred" regimens: efavirenz/emtricitabine/tenofovir FDC (600 mg/200 mg/300 mg); atazanavir/ritonavir (150 mg/100 mg) plus emtricitabine/tenofovir (200 mg/300 mg); darunavir/ritonavir (400 mg/100 mg) plus emtricitabine/tenofovir (200 mg/300 mg); and raltegravir (400 mg) plus emtricitabine/tenofovir (200 mg/300 mg). The manufacturer reported the cost of the darunavir/cobicistat FDC is lower than all preferred (and alternative) regimens.

2. KEY LIMITATIONS

2.1 Evidence Supporting Equivalent Clinical Efficacy

There are no head-to-head trials for the darunavir/cobicistat FDC, as clinical information focuses on bioequivalence. Consequently, the assessment of its effectiveness compared with other treatments and, as a result, its comparative cost-effectiveness, is uncertain. Moreover, the manufacturer assumed cobicistat-boosted and ritonavir-boosted darunavir to be clinically equivalent. This assumption was based on the results of their naive indirect comparison, which included only single-group trials. Given the lack of good-quality comparative clinical evidence, there is significant uncertainty in the manufacturer's economic analysis regarding the assumption of clinical equivalence; this assumption was the reason why the manufacturer chose to perform a cost-minimization analysis.

2.2 Exclusion of Relevant Comparator

Atazanavir boosted with ritonavir was not considered in the manufacturer's base-case analysis. This comparator is a recommended initial ART regimen (with appropriate backbone drugs) in the HHS guidelines.[7] Further, the CADTH Common Drug Review (CDR) clinical expert indicated that the availability of a darunavir/cobicistat FDC would significantly displace the use of atazanavir boosted with ritonavir, in addition to the use of darunavir boosted with ritonavir. Inclusion of this comparator would allow for a more complete cost comparison.

2.3 Cost Comparison of Darunavir/Cobicistat FDC Versus Other Antiretrovirals

The cost comparison of the darunavir/cobicistat FDC versus other antiretrovirals was not adequate, as the manufacturer did not include backbone regimens and the associated costs for the darunavir/cobicistat FDC, while the drugs being compared included the complete regimen (full regimen costs). This overestimates the cost savings associated with the darunavir/cobicistat FDC when compared with other antiretrovirals, especially in the case of regimens that are listed as first-line treatment options in HIV-1 in infected adults.

2.4 Comparators Based on 2013 HHS Guidelines

The manufacturer's choice of comparators was based on the HHS guidelines from February 2013.[6] The Guidelines were recently updated in May 2014,[7] but may not have been available at the time the manufacturer conducted their analysis. The May 2014 update to includes several changes to the recommended and alternative regimens for treatment-naive and treatment-experienced patients, affecting the interpretation of the cost savings associated with the darunavir/cobicistat FDC versus other ART regimens.

3. ISSUES FOR CONSIDERATION

In a region where genotypic resistance testing is not available or may be limited, patients who are treatment-experienced may not be able to be tested for DRV RAMs. In this case, the darunavir/cobicistat FDC should be given to only treatment-naive patients.

While the availability of regimens for co-formulated FDCs offers benefits to patients in terms of convenience, and potentially adherence, it presents challenges to generic entrants as individual drug patents expire.

4. RESULTS AND CONCLUSIONS

The daily cost of the darunavir/cobicistat FDC when used in combination with the backbone emtricitabine/ tenofovir ($50) is similar to that of both the initial ART PI-based regimens recommended in the HHS guidelines (darunavir boosted with ritonavir and atazanavir boosted with ritonavir, when used in combination with emtricitabine/tenofovir). Alternatively, when compared with first-line single-tablet integrase strand transfer inhibitors or non-nucleoside reverse transcriptase inhibitor regimens, darunavir/cobicistat plus emtricitabine/tenofovir is more expensive than rilpivirine/tenofovir/ emtricitabine ($9 more costly), efavirenz/tenofovir/emtricitabine ($8 more costly), and elvitegravir/ cobicistat/tenofovir/emtricitabine ($6 more costly).

As identified by the clinical expert, when the backbone regimen emtricitabine/tenofovir cannot be used (due to renal dysfunction or otherwise), the darunavir/cobicistat FDC may be used in combination with abacavir/lamivudine. The cost of this regimen ($47) is equivalent to the other ART PI-based regimens with the same backbone drugs that are either recommended for patients with a pre-ART plasma HIV RNA of less than 100,000 copies/mL, or alternative initial ART regimens.

5. COST-COMPARISON TABLE

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST-COMPARISON TABLE FOR HIV ANTIRETROVIRAL DRUGS IN TREATMENT-NAIVE ADULT PATIENTS – PROTEASE INHIBITORS

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Daily Cost ($)	Frequency of Use (Per Day)	Number of Pills Per Day
Darunavir/cobicistat + Emtricitabine/tenofovir	**800 mg/150 mg 200 mg/300 mg**	**Tab**	**23.1720[a] 28.0355**	**800 mg daily 1 tablet daily**	**51.21**	**1**	**2**
Darunavir/cobicistat + Abacavir/lamivudine	**800 mg/150 mg 600 mg/300 mg**	**Tab**	**23.1720[a] 23.6191**	**800 mg daily 1 tablet daily**	**46.79**	**1**	**2**
Recommended initial ART regimen options for all patients							
Darunavir (with ritonavir) + Emtricitabine/tenofovir	800 mg[b] (100 mg) 200 mg/300 mg	Tab	21.7160 (1.4671) 28.0355	800 mg + 100 mg daily 1 tablet daily	51.22	1	3
Atazanavir (with ritonavir) + Emtricitabine/tenofovir	300 mg[b] (100 mg) 200 mg/300 mg	Cap Tab	22.4330[c] (1.4671) 28.0355	300 mg + 100 mg daily 1 tablet daily	51.94	1	3
Recommended ART regimens for patients with pre-ART plasma HIV RNA < 100,000 copies/mL							
Atazanavir (with ritonavir) + Abacavir/lamivudine	300 mg[b] (100 mg) 600 mg/300 mg	Cap Tab	22.4330[c] (1.4671) 23.6191	300 mg + 100 mg daily 1 tablet daily	47.52	1	3
Alternative initial ART regimen options							
Darunavir (with ritonavir) + Abacavir/lamivudine	800 mg[b] (100 mg) 600 mg/300 mg	Tab	21.7160 (1.4671) 23.6191	800 mg + 100 mg daily 1 tablet daily	46.80	1	3
Lopinavir/ ritonavir + Abacavir/lamivudine	200 mg/50 mg[b] 600 mg/300 mg	Tab	5.5197 23.6191	400 mg/ 100 mg twice daily[d] 1 tablet daily	45.70	2[d]	5

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Daily Cost ($)	Frequency of Use (Per Day)	Number of Pills Per Day
Lopinavir/ ritonavir	200 mg/50 mg[b]	Tab	5.5197	400 mg/ 100 mg twice daily[d]	50.11	2[d]	5
+							
Emtricitabine/tenofovir	200 mg/300 mg		28.0355	1 tablet daily			

ART = antiretroviral therapy; cap = capsule; HHS = US Department of Health and Human Services; RNA = ribonucleic acid; tab = tablet.
[a] Manufacturer-submitted price.
[b] Available in other strengths not listed.
[c] Obtained from the Saskatchewan Formulary (accessed January 2015).
[d] Can also be taken as 800 mg/200 mg once daily (not recommend for pregnant patients).
Note: Based on the 2014 DHHS guidelines for the use of antiretroviral drugs in HIV-1–infected adults and adolescents.[7] Unless otherwise indicated, all prices are from the Ontario Drug Benefit Formulary (accessed January 2015) and do not include dispensing fees.

APPENDIX 1: COST COMPARISON — OTHER REGIMENS

TABLE 2: COST-COMPARISON TABLE FOR HIV ANTIRETROVIRAL DRUGS IN TREATMENT-NAIVE ADULT PATIENTS — OTHER REGIMENS

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Daily Cost ($)	Frequency of Use (Per Day)	Number of Pills Per Day
Darunavir/cobicistat + Emtricitabine/tenofovir	**800 mg/150 mg 200 mg/300 mg**	**Tab**	**23.1720[a] 28.0355**	**800 mg daily 1 tablet daily**	**51.21**	**1**	**2**
Darunavir/cobicistat + Abacavir/lamivudine	**800 mg/150 mg 600 mg/300 mg**	**Tab**	**23.1720[a] 23.6191**	**800 mg daily 1 tablet daily**	**46.79**	**1**	**2**
Recommended initial ART regimen options for all patients							
Efavirenz/tenofovir/ emtricitabine[a]	600 mg/300 mg /20 mg	Tab	43.2478	1 tablet daily	43.25	1	1
Dolutegravir + Abacavir/lamivudine[b]	50 mg 600 mg/300 mg	Tab	602.18[c] 23.6191	50 mg daily (or 50 mg twice daily[d]) 1 tablet daily	625.80 (or 1227.98)	1 (or 2)	2 (or 3)
Dolutegravir + Emtricitabine/tenofovir[b]	50 mg 200 mg/300 mg	Tab	602.18[c] 28.0355	50 mg daily (or 50 mg twice daily[d]) 1 tablet daily	630.22 (or 1,232.40)	1 (or 2)	2 (or 3)
Elvitegravir/cobicistat/ tenofovir/emtricitabine[b]	150 mg/15 mg /200 mg/300 mg	Tab	45.5200	1 tablet daily	45.52	1	1
Raltegravir + Emtricitabine/tenofovir[b]	400 mg 200 mg/300 mg	Tab	13.5000 28.0355	400 mg twice daily 1 tablet daily	55.04	2	3
Recommended ART regimens for patients with pre-ART plasma HIV RNA < 100,000 copies/mL							
Efavirenz + Abacavir/lamivudine[a]	600 mg[e] 600 mg/300 mg	Tab	3.8030 23.6191	600 mg daily 1 tablet daily	27.42	1	2

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Daily Cost ($)	Frequency of Use (Per Day)	Number of Pills Per Day
Rilpivirine/tenofovir/ emtricitabine[a]	200 mg/25 mg /300 mg	Tab	42.5305	1 tablet daily	42.53	1	1
Alternative Initial ART regimen options							
Raltegravir + Abacavir/lamivudine[b]	400 mg 600 mg/300 mg	Tab	13.5000 23.6191	400 mg twice daily 1 tablet daily	50.62	2	3

ART = antiretroviral therapy; HHS = Health and Human Services; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; RNA = ribonucleic acid; tab = tablet.
[a] NNRTI-based regimen.
[b] INSTI-based regimen.
[c] Obtained from McKesson Canada (accessed January 2015).
[d] For treatment-experienced, integrase inhibitor–resistant patients.
[e] Also available in other strengths not listed here.
Note: Based on the 2014 HHS guidelines for the use of antiretroviral drugs in HIV-1–infected adults and adolescents.[7] Unless otherwise indicated, all prices are from the Ontario Drug Benefit Formulary (accessed January 2015) and do not include dispensing fees.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	**Prezcobix (darunavir/cobicistat 800 mg/150 mg, FDC product)**
Treatment	Darunavir/cobicistat 800 mg/150 mg taken once daily with food in combination with other antiretroviral drugs for the treatment of HIV infection
Comparator	Prezista (darunavir 800 mg), boosted with ritonavir 100 mg
Study Question	To determine the cost-effectiveness of darunavir/cobicistat 800 mg/150 mg FDC compared with single-agent darunavir (800 mg) and single-agent ritonavir (150 mg) for treatment-naive and treatment-experienced HIV-1–infected patients.
Type of Economic Evaluation	Cost-minimization analysis
Target Population	ART-naive adults and ART-experienced adults with no DRV RAMs
Perspective	Ontario public drug program
Outcomes Considered	C_{max} and AUC_{24h}
Key Data Sources	
Cost	• Cost of darunavir/cobicistat 800 mg/150 mg FDC obtained from the manufacturer • Cost of other ARTs obtained from the Ontario Drug Benefit[4] • Administration costs, monitoring costs, and costs associated with adverse events were not included • All costs excluded markup and dispensing fees
Clinical Efficacy	Based on a manufacturer-submitted naive indirect comparison that compared the darunavir/cobicistat 800 mg/150 mg FDC with darunavir 800 mg boosted with ritonavir 100 mg. This was conducted using data from a phase 3 single-group open-label study (GS-US-216-0130) and two registration studies for darunavir (ODIN and ARTEMIS). A multivariate analysis was employed, and the data were treated as observational. Non-inferior efficacy was demonstrated between the two, both at a 10% and 12% non-inferiority margin. As there are no head-to-head trials, clinical evidence is primarily based on bioequivalence studies.
Harms	GS-US-216-0130, phase 3 single-group open-label study[3]
Time Horizon	Daily
Results for Base Case	• Annual daily drug cost of the darunavir/cobicistat 800 mg/150 mg FDC was equivalent to the combined costs of the individual drugs (darunavir [800 mg] boosted with ritonavir [100 mg]). • Darunavir/cobicistat 800 mg/150 mg FDC was less costly than all other preferred (recommended) and alternative ARVs regimens outlined by the 2013 HHS guidelines for the management of HIV-1 infection. • Darunavir/cobicistat 800 mg/150 mg FDC was more costly than four regimens identified as "other – less satisfactory" in the 2013 HHS guidelines.

ART = antiretroviral therapy; ARV = antiretroviral; HHS = Health and Human Services; DRV = darunavir; FDC = fixed-dose combination; RAM = resistance-associated mutation.

Manufacturer's Results

The manufacturer reported that the price of the darunavir/cobicistat 800 mg/150 mg FDC is equivalent to that of the existing single-drug formulation of darunavir (800 mg) with the boosting drug, ritonavir (100 mg). The average daily cost for both the darunavir/cobicistat 800 mg/150 mg FDC and the combination of the individual drugs, darunavir (800 mg) and ritonavir (100 mg), is $23 (Table 4). Though it may not be a cost-saving alternative, the manufacturer reported that treatment with the FDC reduces pill burden, in addition to enhancing patient convenience.

TABLE 4: MANUFACTURER'S BASE-CASE ANALYSIS RESULTS

Drug/Comparator	Strength	Price ($)[a]	Average Daily Use	Average Daily Drug Cost ($)	Frequency of Use (Per Day)	Number of Pills (Per Day)[b]
Darunavir/cobicistat	800 mg/150 mg	23.1720	800 mg/150 mg QD	23.1720	1	1
Darunavir + Ritonavir	800 mg 100 mg	21.7160 1.4670	800 mg/100 mg QD	23.1831	1	2

QD = once daily.
[a] Price of comparator drugs obtained from the 2014 Ontario Drug Benefit Formulary/Comparative Drug Index.
[b] Does not include backbone regimen.
Source: Adapted from manufacturer's pharmacoeconomic submission.

The manufacturer also conducted a cost-comparison analysis comparing the darunavir/cobicistat 800 mg/150 mg FDC with the "preferred" (recommended), "alternative," and "other" regimens outlined in the HHS's 2013 guidelines for the management of HIV-1 infection (Table 5). The manufacturer reported that the darunavir/cobicistat 800 mg/150 mg FDC is associated with lower average daily drug costs than all preferred and alternative regimens. Additionally, the manufacturer reported that darunavir/cobicistat 800 mg/150 mg FDC is more expensive per day than four regimens: nevirapine plus lamivudine/zidovudine ($15 more costly); efavirenz plus lamivudine/zidovudine ($9 more costly); atazanavir plus lamivudine/zidovudine ($5 more costly); and rilpivirine plus lamivudine/zidovudine ($3 more costly). In the 2013 HHS guidelines, these regimen options are considered "regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens."[6] It should be noted that several of the average daily drug cost calculations conducted by the manufacturer presented in Table 5 were incorrect, primarily due to outdated Ontario Drug Benefit Formulary prices.

TABLE 5: MANUFACTURER'S COST COMPARISON OF DARUNAVIR/COBICISTAT FDC VERSUS OTHER ANTIVIRALS

Drug/Comparator	Strength	Price ($)[a]	Average Daily Use[b]	Average Daily Drug Cost ($)	Frequency of Use (Per Day)	Number of Pills Per Day[c]
Preferred regimens[d]						
Efavirenz/emtricitabine /tenofovir	600 mg/200 mg /300 mg	42.6443	600 mg/200 mg /300 mg QD	42.64	1	1
Atazanavir/ritonavir + Emtricitabine/tenofovir	150 mg (100 mg) + 200 mg/300 mg	11.3542 (1.4671) + 27.4320	300 mg/100 mg QD + 200 mg/300 mg QD	51.61	1	4
Darunavir/ritonavir + Emtricitabine/tenofovir	400 mg (100 mg) + 200 mg/300 mg	10.8580 (1.4671) + 27.4320	800 mg/100 mg QD + 200 mg/300 mg QD	50.62	1	4
Raltegravir + Emtricitabine/tenofovir	400 mg + 200 mg/300 mg	13.5000 + 27.4320	400 mg BID + 200 mg/300 mg QD	54.43	2	3
Alternative regimens[d]						
Efavirenz + Abacavir/lamivudine	600 mg + 600 mg/300 mg	8.4984 + 23.6191	600 mg QD + 600 mg/300 mg QD	32.12	1	2
Emtricitabine/rilpivirine/tenofovir	200 mg/25 mg /300 mg	41.6500	200 mg/25 mg/ 300 mg QD	41.65	1	1
Rilpivirine + Abacavir/lamivudine	25 mg + 600 mg/300 mg	14.4950 + 23.6191	25 mg QD + 600 mg/300 mg QD	38.11	1	2
Atazanavir/ritonavir + Abacavir/lamivudine	150 mg (100 mg) + 600 mg/300 mg	11.3542 (1.4671) + 23.6191	300 mg/100 mg QD + 600 mg/300 mg QD	36.44	1	2
Darunavir/ritonavir + Abacavir/lamivudine	400 mg (100) mg + 600 mg/300 mg	10.8580 (1.4671) + 23.6191	800 mg/100 mg QD + 600 mg/300 mg QD	46.80	1	4

Drug/Comparator	Strength	Price ($)[a]	Average Daily Use[b]	Average Daily Drug Cost ($)	Frequency of Use (Per Day)	Number of Pills Per Day[c]
Fosamprenavir/ ritonavir + Abacavir/lamivudine	700 mg (100 mg) + 600 mg/300 mg	8.2076 (1.4671) + 23.6191	1,400 mg/200 mg QD + 600 mg/300 mg QD	42.97	1	5
Fosamprenavir/ ritonavir + Emtricitabine/tenofovir	700 mg (100) mg + 200 mg/300 mg	8.2076 (1.4671) + 27.4320	1,400 mg/200 mg QD + 200 mg/300 mg QD	46.78	1	5
Lopinavir/ritonavir + Abacavir/lamivudine	200 mg/50 mg + 600 mg/300 mg	5.5197 + 23.6191	800 mg/200 mg QD + 600 mg/300 mg QD	45.70	1	5
Lopinavir/ritonavir + Emtricitabine/tenofovir	200 mg/50 mg + 200 mg/300 mg	5.5197 + 27.4320	800 mg/200 mg QD + 200 mg/300 mg QD	49.51	1	5
Elvitegravir/cobicistat/ Emtricitabine/tenofovir	150 mg/150 mg /200 mg/300 mg	45.5200	150 mg/150 mg /200 mg/300 mg QD	45.52	1	1
Raltegravir + Abacavir/lamivudine	400 mg + 600 mg/300 mg	13.5000 + 23.6191	400 mg BID + 600 mg/300 mg QD	50.62	2	3
Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens[d]						
Efavirenz + Lamivudine/zidovudine	600 mg + 150 mg/300 mg	8.4984 + 2.6103	600 mg QD + 150 mg/300 mg BID	13.72	2	3
Nevirapine + Abacavir/lamivudine	200 mg + 600 mg/300 mg	1.2346 + 23.6191	200 mg BID + 600 mg/300 mg QD	26.09	2	3

ARV = antiretroviral; BID = twice a day; FDC = fixed-dose combination; HHS = Health and Human Services; QD = once daily.

[a] Price of comparator drugs obtained from the 2014 Ontario Drug Benefit/Comparative Drug Index, except the pricing for maraviroc and zidovudine, which was obtained from the Régie de l'assurance du Québec Liste de médicaments 2014.

[b] Recommended dosing obtained from respective brand name product monographs.

[c] Does not include backbone regimen.

[d] Based on the 2013 guidelines developed by the Panel on Antiretroviral Guidelines for Adults and Adolescents, and the US Department of Health and Human Services (HHS).

Source: Adapted from the manufacturer's pharmacoeconomic submission based on the 2013 HHS guidelines on the use of ARV drugs in HIV-1–infected adults and adolescents.[6]

TABLE 6: KEY LIMITATIONS

Identified Limitation	Description	Implication
Evidence supporting equivalent clinical efficacy	There are no head-to-head trials comparing the darunavir/cobicistat FDC with any other ART regimens. The clinical data that does exist focuses primarily on bioequivalence. To attempt a comparison, the manufacturer conducted a naive indirect comparison[2] using data from single-group trials. Further, there were two other key limitations as identified in the *CDR Clinical Review Report* (Appendix 6). These included: • Lack of clarity around the use of a 10% to 12% inferiority margin when comparing booster drugs (cobicistat versus ritonavir) • Lack of adequately balanced comparison groups for baseline and disease characteristics.	Clinical equivalence for the darunavir/cobicistat FDC compared with relevant comparators cannot be established. This is required as the basis to conduct a cost-minimization analysis.
Exclusion of atazanavir boosted with ritonavir as a comparator	The manufacturer did not include the PI regimen atazanavir boosted with ritonavir as a comparator in their base-case analysis. The use of this regimen (with appropriate backbone drugs) would be significantly affected by the availability of the darunavir/cobicistat FDC, as outlined by the CDR clinical expert. Further, it is listed as a recommended initial ARV PI regimen (with emtricitabine/tenofovir FDC backbone) option in the HHS guidelines for the management of HIV-1 infection.[6]	The inclusion of this regimen would have provided for a more complete base-case analysis.
Cost-comparison analysis of darunavir/cobicistat FDC versus other ARVs	The manufacturer conducted a cost-comparison analysis of darunavir/cobicistat FDC versus other ARVs as seen in Table 2 of the manufacturer's PE submission.[2] These ARVs were based on the 2013 HHS guidelines.[6] This comparison is incorrect. The manufacturer failed to include a backbone regimen (and subsequent costs) with the darunavir/cobicistat FDC; the ARVs that were compared took into account the entire regimen, which included the backbone drugs (and subsequent costs).	This overestimates the cost savings associated with the darunavir/cobicistat FDC when compared with other ARVs. This is especially significant for regimens that are preferred first-line options in the treatment of HIV-1 in infected adults, as outlined in the HHS guidelines.
Use of 2013 HHS guidelines for the management of HIV-1 infection	The manufacturer used the 2013 HHS guidelines for the management of HIV-1 infection; however, the guidelines were updated in 2014.	This affects the manufacturer's cost-comparison analysis (e.g., cost savings interpretation) as the recommendation for several regimens was changed in the 2014 update.

ART = antiretroviral therapy; ARV = antiretroviral; CDR = CADTH Common Drug Review; FDC = fixed-dose combination; HHS = Health and Human Services; PE = pharmacoeconomic; PI = protease inhibitor.

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