Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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darunavir 800mg, cobicistat 150mg film-coated tablet (Rezolsta®)

SMC No. (1081/15)

Janssen-Cilag Ltd.

10 July 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

darunavir/cobicistat (Rezolsta®) is accepted for use within NHS Scotland.

Indication under review: In combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years or older. Genotypic testing should guide its use.

Pharmacokinetic studies have demonstrated that darunavir/cobicistat is bioequivalent (in terms of darunavir exposure) to ritonavir-boosted darunavir. No comparative efficacy studies have been reported.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Indication

In combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years or older. Genotypic testing should guide the use of Rezolsta®.

Dosing Information

Therapy should be initiated by a healthcare provider experienced in the management of HIV infection. After therapy has been initiated, patients should not alter the dosage or discontinue therapy without the instruction of their healthcare provider. Tablets should be swallowed whole within 30 minutes after completion of a meal.

Anti-retroviral treatment (ART)-naïve patients
One tablet once daily taken with food.

ART-experienced patients
One tablet once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA <100,000copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

Product availability date

December 2014

Summary of evidence on comparative efficacy

Rezolsta® is a fixed-dose combination tablet of two medicines (one antiretroviral agent, darunavir [DRV] and a pharmacokinetic booster, cobicistat [COBI]). DRV is a protease inhibitor whereas COBI has no anti-viral activity but is an inhibitor of the cytochrome P450 3A sub-family of metabolic enzymes. COBI enhances (boosts) the systemic exposure of CYP3A substrates such as DRV.[1]

In relation to the management of adults with HIV infection, SMC has published advice for both components of this fixed-dose combination tablet. Darunavir has been accepted for use in NHS Scotland for both antiretroviral treatment (ART)-naive and ART-experienced patients, whereas COBI, as a pharmacokinetic enhancer of darunavir or atazanavir, has not been recommended for use due to non-submission. The fixed-dose combination, Stribild® has been accepted for use in the management of HIV infection; this contains COBI as a pharmacokinetic enhancer of the integrase inhibitor elvitegravir.

There is no direct evidence of comparative clinical efficacy for DRV/COBI. Two phase I open-label, randomised crossover studies investigating the pharmacokinetics of DRV/COBI compared with ritonavir-boosted DRV (DRV/r) in healthy volunteers were pivotal in demonstrating bioequivalence, which underpinned the extrapolation of clinical efficacy data from the DRV/r development programme.[2,3] These studies (GS-US-216-0115 and TMC114IFD001) established that DRV/COBI (either as individual components or in a fixed-dose combination tablet) is bioequivalent to DRV/r in terms of the exposure (maximum concentration [C_{max}]and area under

the time-concentration curve over 24 hours [AUC_{24h}]) to DRV over the 24-hour dosing period. The concentration of DRV at the end of the dosing interval (C_{tau}) was approximately 30% lower for subjects given DRV/COBI compared with DRV/r. However the European Medicines Agency (EMA) was satisfied that, based on analyses of pharmacokinetic/pharmacodynamic data, that lower C_{tau} would not lead to a clinically important effect on virological response.[2-4] A third pharmacokinetic study (TMC114IFD1003) compared DRV/COBI administered as individual agents with DRV/COBI when given as the marketed fixed-dose combination tablet.[5] Under fed conditions (as per the licensed dosage recommendations), bioequivalence was demonstrated in terms of darunavir C_{max} and AUC.[4,5]

An open-label, single-arm, phase IIIb study (NCT01440569) evaluated the safety, tolerability and efficacy of DRV/COBI in 313 adults with HIV-1 infection, viral load >1,000 copies/mL with no DRV resistance-associated mutations (RAMs).[6] All patients received DRV and COBI as individual tablets (2x400mg DRV, 1x150mg COBI) in combination with investigator-selected backbone of two active nucleos(t)ide reverse transcriptase inhibitors (NRTIs). The primary outcome was a safety endpoint and is reported in the safety section below.

Key efficacy outcomes included the virological response (defined as viral load <50copies/mL). In the intention to treat population (all randomised patients who took at least one dose of DRV and COBI), the virological response rate (Food and Drug Administration [FDA] snapshot analysis) was 82% (95% confidence interval [CI]: 78 to 87) at week 24 and 81% (95% CI: 76 to 85) at week 48. When assessed using the Time to Loss of Virological Response (TLOVR) algorithm, the virological response rate at week 48 was also 81%.[6]

Fifteen patients underwent post-baseline genotypic resistance testing because of either sub-optimal virological response (n=3), virological rebound (n=8) or discontinuation with viral load ≥400 copies/mL (n=4). Two patients developed the M184V RAM, associated with phenotypic resistance to lamivudine and emtricitabine.[6]

Immunological response to treatment was assessed by changes in the CD4-cell count. In an observed dataset (n=276), CD4 cell count increased from baseline (median 361 cells/mm^3) by a median 167 cells/mm^3 (range: -193 to 1,086) after 48 weeks. Adherence rates (measured by pill count) were high; median adherence was 100%, with 96% of patients achieving at least 90% adherence rate. This was true in both the overall and treatment-naive populations.[6]

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details.

In the phase IIIb single-arm, 48-week study, the incidence of any grade 3 (severe) or 4 (life-threatening) adverse events(AE) through to week 24; were reported by 6% (18/313) of patients. This was the primary endpoint of the study.[6]

Drug-related adverse events (AEs) were experienced by 41% (128/313) of patients and AEs led to discontinuation in 16 patients. AEs leading to discontinuation in more than one patient were: maculo-papular rash (n=3), rash (n=3), nausea (n=2) and hypersensitivity (n=2). The most common drug-related AEs experienced through to week 48 were gastro-intestinal: diarrhoea (15%), nausea (14%), and flatulence (4.2%). Headache was also reported by 4.2% of patients.

Consistent with cobicistat's inhibition of creatinine secretion, serum creatinine levels increased for the duration of the study (median change of 0.10mg/dL [8.84 micromol/L] at week 2 and median change of 0.09mg/dL [7.96 micromol/L] at week 48).[6]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

DRV/COBI is the first once daily boosted protease inhibitor (PI) formulated as a fixed dose combination. In ART-naive patients, UK guidance recommends that a backbone of two NRTIs are combined with a third active agent, either a ritonavir-boosted protease inhibitor, an non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor. The NRTI backbone of preference is tenofovir/emtricitabine. Preferred boosted protease inhibitors are DRV/r or ritonavir-boosted atazanavir (ATV/r); the preferred NNRTI is efavirenz and preferred integrase inhibitors are raltegravir or elvitegravir/cobicistat. ART-experienced patients will have treatment regimen guided by the presence of RAMs amongst other factors such as drug interactions, co-morbidities and side effect profiles.[8]

There are pharmacokinetic bioequivalence studies relative to an active comparator. Pharmacokinetic studies bridge between DRV/COBI as a fixed-dose combination to DRV boosted by COBI (as separate dosage forms) and to DRV/r. However, there are no direct comparative data for clinical outcomes. The 48-week non-comparative study in patients with HIV infection used an accepted and standard surrogate outcome (virological response) to evaluate the efficacy of DRV/COBI.

Evidence is limited for treatment of patients who are ART-experienced. Patients with ART-experience comprised 18/313 patients in the phase IIIb study population, and at least nine would not be eligible for DRV/COBI under its licence since their baseline viral load was >100,000 copies/mL.[6]

To supplement the bioequivalence data for DRV/COBI and DRV/r, a patient level naive indirect comparison was conducted. It compared DRV/COBI with DRV/r in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adults aged 18 years or older.[9] A total of three studies were included, with data from two DRV/r studies pooled. The primary endpoint was virological response at week 48. The odds ratios were adjusted for potential confounding variables in a logistic regression model using co-variates: age, gender, race, baseline CD4 cell count, baseline viral load, HIV disease status, and previous antiretroviral use. The results suggest that the two treatments have similar virological outcomes at week 48.

Given the naïve methodology employed the results should be interpreted with some caution. A network meta-analysis would have been preferred, but the design of the DRV/COBI study did not allow for this to be carried out. Strength of the analysis is the use of logistic regression, and patient level data. However, potentially relevant studies may have been excluded from the analysis due to the lack of patient level data available to the company. Another limitation of the analysis is the limited data for ART-experienced patients treated with DRV/COBI.

The results of the ARDENT study, in which 1,809 ART-naive patients were randomly assigned to receive DRV/r, ATV/r or raltegravir in combination with tenofovir/emtricitabine, support the economic case in comparison with ATV/r. In this 96-week study DRV/r and ATV/r met the pre-

specified criteria for equivalence in terms of incidence of virologic failure; however DRV/r was found to be superior to ATV/r in terms of tolerability failure.[10]

Clinical experts consulted by SMC considered that the place in therapy of DRV/COBI is in patients intolerant of ritonavir-associated side effects, although they note that both ritonavir and COBI are associated with significant drug-interactions.

Introduction of the fixed dose combination tablet reduces the pill burden of patients managed with boosted protease inhibitors; all other boosted protease inhibitors require at least two tablets per day (e.g. 1x300mg atazanavir plus 1x100mg ritonavir).

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis which compared DRV/COBI against DRV/r and ATV/r for the treatment of HIV-1 infection in adults aged 18 years or older.

The company used a Markov model in order to perform the analysis and the time horizon used in the evaluation was 10 years.

In terms of model structure patients entered the model in an on treatment health state where patients received DRV/COBI, DRV/r, and ATV/r. Patients could transition to the off treatment state due to treatment discontinuation, or death. Once patients had left the on treatment state they could not return to this health state and patients who were in the off treatment state could also transition to death.

The sources of the clinical data used in the model included the Office of National Statistics, Public Health England and the NCT01440569 study. The Office of National Statistics and Public Health England informed the background mortality and HIV specific mortality estimates used in the model. The NCT01440569 study provided estimates of the treatment discontinuation rates used in the cost-minimisation analysis.

Data to support the comparable efficacy and safety of DRV/COBI and DRV/r were derived from the TMC114IFD1001 and TMC114IFD1003 bioequivalence studies, as well as an indirect comparison. The comparable efficacy and safety of DRV/COBI and ATV/r was based on the ARDENT study.

In terms of costs, medicines costs only were included in the analysis.

The results of the cost-minimisation analysis indicated that DRV/COBI and DRV/r generated equal costs of £15,550 per patient. DRV/COBI was less costly than ATV/r as ATV/r generated a cost of £15,824 per patient. This resulted in a saving of £274 per patient for DRV/COBI versus ATV/r.

The company provided sensitivity analyses which reduced the discontinuation rate to 6% and 7.42%, changed the discount rate and increased the time horizon to 20 years. In all analyses the cost per patient of DRV/COBI remained equal to DRV/r. In addition, DRV/COBI remained less costly than ATV/r in all the sensitivity analyses described above.

The main weaknesses were as follows:

- The appropriateness of selecting a cost-minimisation analysis as the relevant format of the economic analysis is dependent on demonstrating the comparable efficacy and safety of the treatments under review. In relation to the comparison versus DRV/r the company had assumed that bioequivalence demonstrated through the clinical studies translated into comparable efficacy. In addition, there were some weaknesses with the supporting indirect comparison. Also no direct head to head data were available for the comparison versus ATV/r and comparable efficacy and safety was demonstrated indirectly through a comparison of DRV/r and ATV/r. However, on balance the evidence provided by the company was considered sufficiently robust to support the cost-minimisation analysis, with DRV/r as the primary comparator.
- The choice of a Markov model structure may not have been appropriate for a simple cost-minimisation analysis where the main differences between the medicines is the unit costs of the medicines. The company also provided a simple analysis that focused on the one year cost of the medicines and this demonstrated that DRV/COBI was equivalent cost to DRV/r and cost saving versus ATV/r.
- The economic analysis focussed on medicines costs only. However SMC clinical expert response had suggested that monitoring, patient education and pharmacy time to review medicine interactions may also be relevant to the analysis. The company response indicated that monitoring costs were not included in the analysis as no difference in monitoring was expected between the treatments being compared. Following consideration of additional SMC expert responses, monitoring, patient education and pharmacy time costs were not considered to differ for the comparators in the analysis.

Despite these issues the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from The Terence Higgins Trust, a registered charity.

- The Terence Higgins Trust has received pharmaceutical company funding in the past two years including from the submitting company.

- Since the advent of highly active ART in the 1990s HIV has changed from being a terminal illness to being a long-term manageable condition for most people. However, there is still a need for long-term support and care for patients. Maintaining treatment adherence in the event of side effects can be challenging. Side effects include diarrhoea, nausea and/or vomiting, headache, tiredness and rashes. Having additional treatment options allows people to transfer medications and find a treatment option that does not have side effects.

- For many patients, treatment will include a combination of more than 3 drugs. Therefore co-formulations are useful. However, depending on the side effect profile and contra-indications not all will be suitable. Darunavir/cobicistat will be a useful addition for patients who cannot tolerate ritonavir and will reduce the number of pills they have to take which is important to patients and their carers.

- Darunavir/cobicistat offers patients another combination treatment which may make it easier for them to adhere to their medicine regimen, benefitting them and their carers alike.

Additional information: guidelines and protocols

The British HIV Association (BHIVA) published guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy in 2012.[8] Post-publication amendments were last updated in June 2014. The guidelines aim to provide guidance on best clinical practice in the treatment and management of adults with HIV infection with ART. The document states that treatment should aim to improve both the physical and psychological wellbeing of people living with HIV and prevent the mortality and morbidity associated with chronic HIV infection, at low cost of drug toxicity.

Patients are recommended to be involved in decisions about their treatments. ART should be initiated if a patient's CD4 cell count ≤350cells/mm^3. ART is also recommended in those with AIDS diagnosis, HIV-associated co-morbidity, or certain co-infections or conditions such as hepatitis B (when CD4 ≤500cells/mm^3) or pregnancy.

It is recommended that in patients who are treatment naive, should be initiated with ART containing two NRTIs plus one of the following: ritonavir-boosted protease inhibitor, NNRTI or an integrase inhibitor.

The preferred ART are noted in the table below. The most appropriate choice for each patient should take into account any co-morbidities and potential adverse effects. The guidelines also include recommendations for treatment-experienced patients who have experienced virological failure which varies depending on the presence and type of drug resistance.

Table: Recommendations for choice of ART in treatment-naive patients.

	NRTI	Third agent
Preferred	Tenofovir and emtricitabine	Atazanavir/ritonavir Darunavir/ritonavir Efavirenz Raltegravir Elvitegravir/cobicistat
Alternative	Abacavir and lamivudine‡*	Rilpivirine ‡ Lopinavir/ritonavir Fosamprenavir/ritonavir Nevirapine†

*Abacavir is contraindicated if HLA-B*57:01 positive. ‡Use recommended only if baseline viral load is <100,000copies/mL. †Nevirapine is not recommended if baseline CD4 cell count is greater than 250/400 cells/mm^3 in women/men.

Additional information: comparators

There are many antiretroviral agents licensed for the treatment of adults with HIV infection. Protease inhibitors recommended in UK guidelines include: darunavir/ritonavir, atazanavir/ritonavir, lopinavir/ritonavir, and fosamprenavir/ritonavir.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Fixed-dose combinations		
darunavir/cobicistat (800/150) Rezolsta®	**one tablet daily**	**3,849**
lopinavir/ritonavir (200/50) Kaletra®	two tablets twice daily	3,463
Individual dosage forms		
atazanavir/ritonavir	atazanavir 300mg once daily + ritonavir 100mg once daily	3,917
darunavir/cobicistat*	darunavir 800mgonce daily + cobicistat 150mg once daily	3,873
darunavir/ritonavir	darunavir 800mg once daily + ritonavir 100mg once daily	3,849
fosamprenavir/ritonavir	fosamprenavir 700mg twice daily + ritonavir 100mg twice daily	3,143

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 April 2015. *cobicistat is not recommended for use in NHS Scotland by SMC.

Additional information: budget impact

The company estimated there to be 2,914 patients eligible in Scotland in both years 1 and 5. Treatment uptake was estimated at 3% in year 1 and 11% in year 5. The discontinuation rate was estimated to be 14%. This resulted in 74 patients treated in year 1 rising to 261 in year 5.

The company estimated the gross medicines budget impact to be £286k in year 1 rising to £1m in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be cost neutral.

References

The undernoted references were supplied with the submission.

1) Janssen-Cilag Ltd. Summary of Product Characteristics: Darunavir/cobicistat (Rezolsta®) film-coated tablets. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 26 November 2014.
2) Kakuda TN, Opsomer M, Timmers M., Iterbeke K, Van De Casteele T, Hillewaert V, et al. Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. The Journal of Clinical Pharmacology. 2014; 54(8): 949-57.
3) Mathias A, Liu HC, Warren D et al. Relative bioavailability andpharmacokinetics of darunavir when boosted with the pharmacoenhancerGS-9350 versus ritonavir. In: Abstracts of the Eleventh InternationalWorkshop on Clinical Pharmacology of HIV Therapy, Sorrento, 2010.Abstract 28.
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5) Kukuda TN, Van De Casteele T, Petrovic R, Neujens M, Salih H, Opsomer M, *et al*. Bioequivalence of a darunavir/cobicistat fixed-dose combination tablet versus single agents and food effect in healthy volunteers. Antiviral Therapy; 2014. doi: 10.3851/IMP2814
6) Tashima K, Crofoot G, Tomaka FL, Kakuda TN, Brochot A, Van de Casteele T, *et al.* Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. AIDS Research and Therapy. 2014; 11(39). doi:10.1186/1742-6405-11-39
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8) Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, *et al.* British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. HIV Medicine. 2014; 15(1): 1-85
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10) Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotojun I, Na LH, Godfrey C, *et al*. Efficacy and Tolerability of 3 Nonnucleoside Reverse Transcriptase Inhibitor-Sparing Anriretroviral Regimens for Treatment-Naive Volunteers Infected with HIV-1. Annals of Internal Medicine. 2014; 161: 461-471.

This assessment is based on data submitted by the applicant company up to and including 10 June 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and

NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.