



# **Clinical Commissioning Policy: Use of cobicistat as a booster in treatment of HIV infection (all ages)**

Reference: NHS England F03/P/b

## NHS England INFORMATION READER BOX

## Directorate

Medical	<b>Commissioning Operations</b>	Patients and Information
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

**Publications Gateway Reference:** 03730

<b>Document Purpose</b>	Policy
<b>Document Name</b>	F03/P/b Cobicistat as a booster in treatment of HIV in adults and adolescents
<b>Author</b>	Specialised Commissioning Team, NHS England
<b>Publication Date</b>	July 2015 – updated September 2018
<b>Target Audience</b>	Local Team Assistant Directors of Specialised Commissioning; IFR Team Leads; Finance Leads; Local Team Pharmacists; Chairs of Clinical Reference Groups; Members of Clinical Reference Groups and registered stakeholders; Acute Trust Chief Executives; Acute Trust Medical Directors; Acute Trust Chief Pharmacists  Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
<b>Additional Circulation List</b>	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
<b>Description</b>	
<b>Cross Reference</b>	
<b>Superseded Docs</b> (if applicable)	
<b>Action Required</b>	
<b>Timing / Deadlines</b> (if applicable)	
<b>Contact Details for further information</b>	england.specialisedcommissioning@nhs.net

**Document Status**

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet. **NB:** The National Health Service Commissioning Board was established on 1 October 2012 as an executive non-departmental public body. Since 1 April 2013, the National Health Service Commissioning Board has used the name NHS England for operational purposes.

## Contents

1	Executive summary .....	4
	Policy Statement .....	4
	Equality Statement .....	4
	Plain Language Summary .....	4
2	Introduction .....	5
3	Definitions .....	5
4	Aim and objectives .....	7
5	Epidemiology and needs assessment.....	7
6	Evidence base .....	8
7	Rationale behind the policy statement .....	9
8	Criteria for commissioning.....	10
9	Patient pathway .....	11
10	Governance arrangements.....	11
11	Mechanism for funding .....	11
12	Audit requirements .....	11
13	Documents which have informed this policy .....	11
14	Links to other policies .....	12
15	Date of review .....	12
	References .....	13

## 1 Executive summary

### Policy Statement

NHS England will commission cobicistat for the treatment of HIV-1 in adults in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

### Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

### Plain Language Summary

Cobicistat is a drug which is used to boost certain other HIV medicines. It provides an alternative to another booster called ritonavir.

Cobicistat is used in the Fixed Dose Combination (FDC) of elvitegravir/cobicistat/emtricitabine/tenofovir-DF, elvitegravir/cobicistat/emtricitabine/tenofovir-AF, darunavir/cobicistat, atazanavir/cobicistat and darunavir/cobicistat/emtricitabine/tenofovir-AF and may become available in other fixed dose combinations in the future.

The evidence suggests cobicistat is equivalent to ritonavir in terms of boosting efficacy.

## 2 Introduction

Cobicistat as a single agent is licensed as a pharmacokinetic enhancer of atazanavir 300mg once daily (OD) or darunavir 800mg OD, as part of antiretroviral combination therapy in HIV-1 infected adults. Some cobicistat-containing products are licensed in adolescents from the age of 12 years and one down to the age of 6 years where indicated for toxicity reasons; use below with age of 18 years is conditional on specific weight requirements. It is given at a dose of 150 mg OD (6). It is also licensed within fixed dose combination tablets listed in section 8; if other cobicistat-containing products are licensed this policy may require revision.

Cobicistat is a strong inhibitor of CYP3A isozymes and increased plasma concentrations of medicinal products metabolised by CYP3A (3, 4), including atazanavir and darunavir, are seen when co-administered with cobicistat.

Unlike ritonavir, cobicistat does not have antiviral activity (4, 7).

## 3 Definitions

The key terms used in this policy and their definitions are:

- **Antiretroviral therapy (ART):** This usually consists of a combination of three antiretroviral drugs. A backbone of two nucleoside reverse transcriptase inhibitors (NRTI) and a 3rd drug or agent from one of the following classes of drugs: non-nucleoside reverse transcriptase inhibitors (NNRTI), ritonavir boosted protease inhibitors (PI/r) and integrase inhibitors (INI).
- **Fixed dose combination (FDC):** Single tablets which combine a number of agents.
- **First line therapy:** Efavirenz is a recommended first line 3rd agent, given in combination with either tenofovir and emtricitabine or lamivudine and abacavir,

## OFFICIAL

and for reasons of clinical effectiveness and cost is the preferred first line option.

- **NRTI/NNRTI backbone and 3<sup>rd</sup> Agent:** These include individual agents often used in fixed dose combinations including: abacavir and lamivudine; tenofovir and emtricitabine; tenofovir with efavirenz and emtricitabine; tenofovir, rilpivirine and emtricitabine; and tenofovir, elvitegravir, cobicistat and emtricitabine.
- **Second line therapy:** The use of alternative 3<sup>rd</sup> agents where efavirenz cannot be used for reasons of potential or actual intolerance or transmitted HIV drug resistance. Alternative 3<sup>rd</sup> agents include: the NNRTIs rilpivirine and nevirapine, the INIs raltegravir, elvitegravir/cobicistat and dolutegravir, and the PIs darunavir/ritonavir and atazanavir/ritonavir. Drug selection depends on side effects profile, tolerability, resistance profile, drug-drug interactions and cost.
- **Viral load:** plasma HIV RNA levels are used to monitor response to antiretroviral therapy. Patients on effective therapy sustain a plasma HIV RNA level of <50 copies/ml (undetectable). Patients who fail to achieve an undetectable viral load or experience a confirmed viral load rebound to above 50 copies/ml are deemed to be experiencing virological failure.
- **Intolerance:** patients who are either assessed to be at high risk of adverse effects or experience adverse effects that will or have led to drug discontinuation are deemed to be intolerant.
- **Stable patients:** patients who continue to experience an undetectable viral load and who are not experiencing any intolerance to their medication are deemed to be stable.

## 4 Aim and objectives

This policy aims to identify the evidence and cost implications of routine commissioning of cobicistat & cobicistat-containing products for specific patient groups.

The objectives are to enable access to cobicistat for patients who are intolerant to the alternative booster, ritonavir, or have a documented indication for a cobicistat-containing regimen that is not covered in existing policies. This is where the clinical evidence supports access and represents good value.

## 5 Epidemiology and needs assessment

## OFFICIAL

HIV treatment has improved greatly over the last two decades and standard of care now involves triple therapy, typically with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus one of the following: a ritonavir-boosted protease inhibitor (PI/r), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI) as per British HIV Association (BHIVA) Treatment guidelines for HIV positive adults (1).

Ritonavir is an HIV protease inhibitor and was initially developed and licensed as an antiretroviral drug to be used in combination therapy. It is no longer used as a specific antiretroviral agent, but is used routinely as a pharmacokinetic enhancer of other HIV protease inhibitors (1, 2). The cytochrome P450 system (CYP) is a family of isozymes which are responsible for the metabolism of many drugs by oxidation. The majority of isozymes are found in the liver but are also found in other tissues including the gastrointestinal tract. Ritonavir has a high affinity for several CYP isozymes and when co-administered with other drugs which are primarily metabolised by CYP3A, results in increased plasma concentrations of the other drug. HIV protease inhibitors are routinely co-administered with ritonavir to increase their plasma concentrations to the therapeutic range required.

Cobicistat is a ritonavir derivative that lacks the backbone hydroxyl group and thus does not have anti HIV protease activity. Similar to ritonavir, it is a strong inhibitor of CYP3A isozymes (3,4) and will increase plasma concentrations of other co-administered drugs which are metabolised by CYP3A. Cobicistat is currently available within the combination drug elvitegravir/cobicistat/emtricitabine/tenofovir (5). Cobicistat as a single drug has also been licensed as a pharmacokinetic enhancer of the HIV protease inhibitors atazanavir (300mg once daily) and darunavir (800 mg once daily) (6).

Development of new ARV medicines often focuses on improvements in tolerability, reductions in toxicity and drug-to-drug interactions.

## 6 Evidence base

## OFFICIAL

The efficacy and safety of cobicistat-boosted atazanavir has been evaluated in comparison with ritonavir boosted atazanavir, in a phase 3, non-inferiority, randomised, double-blind study in treatment naïve patients, for which results to week 48 have been published (7). All patients also received a backbone of emtricitabine and tenofovir.

Atazanavir with cobicistat was shown to be non-inferior to atazanavir with ritonavir in terms of rates of viral suppression at one year and similar outcomes were all seen in sub-group analysis. The side effects profiles and discontinuation rates due to adverse events were similar, and no major tolerability issues were reported (7).

The evidence supporting the use of cobicistat to boost darunavir is limited to one phase 1 study which evaluated the relative bioavailability and pharmacokinetics of darunavir when co-administered with cobicistat versus ritonavir (8.) Cobicistat effectively boosted darunavir plasma levels to a similar degree to ritonavir, with a similar pharmacokinetic profile.

Cobicistat affects tubular secretion of creatinine, by inhibiting renal cation transporters. This results in small increases in serum creatinine and decreases in estimated creatinine clearance. However it does not cause impairment of renal function as actual glomerular filtration rate is not affected (9).

Darunavir/cobicistat/emtricitabine/tenofovir-AF FDC has been studied first-line against Darunavir/cobicistat + tenofovir-DF/emtricitabine demonstrating non-inferior efficacy and significant bone & renal surrogate marker benefits as outlined in the tenofovir-AF policy. Darunavir/cobicistat/emtricitabine/tenofovir-AF FDC has also been studied as a switch option in patients suppressed on a boosted protease inhibitor + tenofovir-DF/emtricitabine, demonstrating non-inferior virological efficacy.

In summary:

- Cobicistat is a ritonavir derivative without anti-HIV protease activity.
- Cobicistat is a potent inhibitor of CYP3A isoenzymes and is licensed as a pharmacokinetic enhancer for the HIV protease inhibitors atazanavir and darunavir.
- The efficacy and safety of atazanavir with cobicistat is similar to that of atazanavir with ritonavir.
- Cobicistat impairs renal tubular secretion of creatinine resulting in small increases in serum creatinine but does not affect glomerular filtration.

## OFFICIAL

Cobicistat has a slightly different inhibitory profile against other CYP isoenzymes, membrane transporter proteins and other cellular enzymes compared to ritonavir. There are some differences in the drug-drug interaction profiles between ritonavir and cobicistat (6). This may be potentially beneficial for some patients, but there is no clinical data to inform this. Of the interaction studies that have been undertaken, most have been performed in combination with elvitegravir. There may potentially be differences when cobicistat is co-administered with either darunavir or atazanavir.

## 7 Rationale behind the policy statement

Safety and efficacy data support the use of cobicistat when combined with darunavir or atazanavir and in patients switching from ritonavir to cobicistat.

The evidence suggests that overall there is no significant clinical advantage of the use of cobicistat over ritonavir as a pharmacokinetic enhancer for atazanavir or darunavir for the treatment of HIV positive adults or adolescents, with the exception of patients with ritonavir intolerance.

A named access programme provided cobicistat for patients who were not able to tolerate ritonavir. In some cases, patients unable to tolerate ritonavir will also be unable to tolerate cobicistat and an alternative regimen will need to be constructed. Use of cobicistat for those unable to tolerate ritonavir can offer an alternative, lower cost regimen.

## 8 Criteria for commissioning

NHS England will routinely commission cobicistat when

- It is part of the Darunavir/cobicistat/emtricitabine/tenofovir-AF FDC utilised under the tenofovir-AF policy
- It is part of the Darunavir/cobicistat/emtricitabine/tenofovir-AF FDC, used outside the tenofovir-AF policy where there is an MDT-documented requirement for this regimen and it falls within regional prescribing guidelines
- It is part of the FDC of elvitegravir/cobicistat/emtricitabine/tenofovir-DF (as set out in the policy F03/P/b), or elvitegravir/cobicistat/emtricitabine/tenofovir-AF (as set out in the policy/circular 16043/P)
- It is part of elvitegravir/cobicistat/emtricitabine/tenofovir-AF where children aged 6-12 years and adolescents from the age of 12 years meet license weight requirements and there is an indication for this product based on

toxicity

- It is used as single agent booster of protease inhibitors in adults and adolescents with HIV (as per its licence) who are clinically appropriate for cobicistat and where the use of a protease inhibitor, if required by regional prescribing guidelines, has been agreed at an MDT; in the absence of cost-based regional prescribing guidelines all protease inhibitor initial therapy or switch decisions should be discussed at MDT

### Exclusions

- Patients prescribed cobicistat who have not been referred to and discussed in the HIV specialist MDT meeting where this is required by regional policy (in the absence of a cost-based regional policy an MDT discussion is required)
- Patients prescribed cobicistat where the decision about their treatment is not recorded.
- Patients taking cobicistat in an FDC other than elvitegravir/cobicistat/emtricitabine/tenofovir where NHS England has not undertaken a review of clinical need and effectiveness, cost and affordability.
- Adolescents from the age of 12 (or in the case of elvitegravir/cobicistat /emtricitabine/tenofovir-AF, also children aged 6-12) who do not meet weight requirement specified in the product license.

### Cost

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

## 9 Patient pathway

Commissioned HIV care and treatment providers who meet the service specification initiate and monitor HIV drug treatment. Prescription and monitoring of cobicistat is in line with the existing patient pathway.

## 10 Governance arrangements

All patients identified who might benefit from cobicistat outside of FDC due to ritonavir intolerance must be referred to and discussed at a specialist HIV MDT and the recommendation recorded. This includes the cohorts identified for routine commissioning as well as any exceptional cases.

## 11 Mechanism for funding

NHS England is responsible for funding the use of all antiretroviral medicines. Trusts are required to separately identify spending on different ART regimens. Funding to the provider will be in accordance with their agreed tariff arrangements.

## 12 Audit requirements

All patients considered for treatment with cobicistat **must** be referred to and discussed in, an HIV specialist MDT. Recommendations for treatment must be recorded.

Commissioners will review the audits.

## 13 Documents which have informed this policy

- Specialised Human Immunodeficiency Virus (HIV) Services (Adult) – service specification B06/S/a
- Clinical commissioning policy statement: Elvitegravir/cobicistat/emtricitabine/tenofovir for the treatment of HIV-1 infection in adults
- Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents

## 14 Links to other policies

Not applicable

## 15 Date of review

## OFFICIAL

This policy will be reviewed when required as further information is received that indicates a review is needed.

## References

1. British HIV Association guidelines for the treatment of HIV positive adults with antiretroviral therapy 2012 (updated 2013). *HIV Medicine*, 2014, 15 (suppl 1): 1-85
2. Ritonavir summary of product characteristics March 2014
3. Xu L, Liu H, Murray B, et al. Cobicistat (GS-9350): a potent and selective inhibitor of human CYP3A as a novel pharmacoenhancer. *ACS Med Chem Lett*, 2010; 1: 209-13
4. Mathias AA, Germab P, Murray BP, et al. Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. *Clin Pharmacol Ther* 2011; 87:322-9
5. B06/PS/a: Clinical commission policy statement: Stribild for the treatment of HIV-1 infection in adults, 2013
6. Gilead Sciences Ltd. Summary of Product Characteristics. Tybost 150mg film-coated tablets. Date of revision of the text: 09/2013. 2013.
7. Gallant J, Gallant, J.E., Koenig, E., Andrade-Villanueva, J., & Chetchotisakd, P. 2013. Cobicistat versus ritonavir as pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *Journal of Infectious Disease*, 208, (1) 32-39 [doi: 10.1093/infdis/jit122]
8. Mathias, A., Liu, H. C., Warren, D, Sekar, V. Relative bioavailability and pharmacokinetics of darunavir when boosted with the pharmacoenhancer GS-9350 versus ritonavir. Abstract #28., 11th International Workshop on Clinical Pharmacology of HIV Therapy. Sorrento, Italy. April 7-9. 2010.
9. German, P., Liu, H.C., Szwarcberg, J., & Hepner, M. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *Journal of Acquired Immune Deficiency Syndromes*, 2012; 61, (1) 32-40
10. Eron JJ, Orkin C, Gallant J et al. A week 48 randomized phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. *AIDS*. 2018 Apr 19.
11. Orkin C, Molina JM, Negredo E et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV*. 2018 Jan;5(1):e23-e34.