NHS England

Clinical Commissioning Policy: Use of cobicistat as a booster in treatment of HIV positive adults and adolescents

Reference: NHS England F03/P/b

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Description	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
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Document Status

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Contents

1 Executive summary

Policy Statement

NHS England will commission cobicistat (Tybost®) 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 new 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 and may become available in other fixed dose combinations in the future.

The evidence suggests it is equivalent to ritonavir although slightly more expensive.

The patients who benefit most from using cobicistat outside of an FDC medicine will be those who are intolerant to ritonavir. Therefore routine commissioning is recommended for this patient group where cobicistat is not used in an FDC.

Where cobicistat is used in other FDCs, the CRG will review the clinical effectiveness and pricing of each combination to advise on clinical need and evidence base, cost and affordability.

2 Introduction

Cobicistat 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. It is given at a dose of 150 mg OD (6).

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). Cobicistat as a single drug has not been reviewed or included in the current BHIVA guidelines. It is part of the combination drug elvitegravir/cobicistat/emtricitabine/tenofovir which is routinely commissioned for certain patient groups and recommendations for the use of this combination has been included in the current BHIVA ART guidelines (1).

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, and for reasons of clinical effectiveness and cost is the preferred first line option.
- **NRTI / NNRTI backbone and 3rd Agent:** These include individual agents often used in fixed dose combinations including: abacavir and lamivudine; tenofvir and emtricitabine; tenofovir with efavirenz and emtricitabine; tenofovir, rilpivirine and emtricitabine; and tenofovir, elvitegravir, cobicistat and emtricitabine.
- **Second line therapy:** The use of alternative 3rd agents where efavirenz cannot be used for reasons of potential or actual intolerance or transmitted HIV drug resistance. Alternative 3rd agents include: the NNRTIs rilpivirine and nevirapine, the INIs raltegravir, elvitegravir/cobicistat and dolutegravir, and the PI/rs 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 (outside of FDCs) for specific patient groups.

The objectives are to enable access to cobicistat – outside of FDCs - for patients who are intolerant to the alternative booster, ritonavir. This is where the clinical evidence supports access and represents good value.

5 Epidemiology and needs assessment

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).

British HIV Association (BHIVA) Treatment guidelines for HIV positive adults currently recommend the following for antiretroviral therapy ART naïve patients: The NRTI backbone: tenofovir and emtricitabine in combination with a third agent: either atazanavir/ritonavir, or darunavir /ritonavir, or efavirenz, or, raltegravir or elvitegravir/cobicistat (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. The HIV protease inhibitors atazanavir, lopinavir, darunavir, saquinavir, and fosamprenavir 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

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 phamacokinetic 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).

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 pharmacokinteic 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.

Cobicistat has a slightly different inhibitory profile against other CYP isozymes, 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 FDC of elvitegravir/cobicistat/emtricitabine/tenofovir (as set out in the policy F03/P/b), or
- It is used as single agent booster of protease inhibitors in adults and adolescents with HIV (as per it's licence) and who have ritonavir intolerance, and
- Ritonavir intolerance has been discussed, agreed and recorded in the HIV specialist multidisciplinary team (MDT) meeting.

Exclusions

- Patients who are not ritonavir intolerant taking cobicistat (unless it is part of the FDC of elvitegravir/cobicistat/emtricitabine/tenofovir)
- Patients prescribed cobicistat who have not been referred to and discussed in the HIV specialist MDT meeting or 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.

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. This policy will be reviewed by the CRG annually.

13 Documents which have informed this policy

- Specialised Human Immunodeficiency Virus (HIV) Services (Adult) – service specification

- 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

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

15 Date of review

This policy will be reviewed in 2016/2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

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