



## **Clinical Commissioning Policy: Bortezomib for the treatment of refractory antibody mediated rejection post kidney transplant**

# OFFICIAL

NHS England INFORMATION READER BOX		
<b>Directorate</b>		
Medical Nursing Finance	<b>Commissioning Operations</b> Trans. & Corp. Ops.	Patients and Information Commissioning Strategy
<b>Publications Gateway Reference: 03707</b>		
<b>Document Purpose</b>	Policy	
<b>Document Name</b>	A07/P/c Bortezomib for treatment of organ rejection post kidney transplantation	
<b>Author</b>	Specialised Commissioning Team, NHS England	
<b>Publication Date</b>	July 2015	
<b>Target Audience</b>	Local Team Assistant Directors of Specialised Commissioning; Regional Team IFR 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	
<b>Additional Circulation List</b>	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing	
<b>Description</b>	NHS England has adopted a policy to not routinely commission this specialised treatment as described in this document.	
<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Superseded Docs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>	jeremyglyde@nhs.net for policy issues	
<b>Document Status</b>		
<p>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. <b>NB:</b> 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.</p>		

## Contents

1	Executive Summary .....	4
	Policy Statement .....	4
	Equality Statement .....	4
	Plain Language Summary .....	4
2	Introduction .....	5
3	Definitions .....	5
4	Aims and Objectives .....	6
5	Epidemiology and Needs Assessment .....	7
6	Evidence Base .....	7
7	Rationale behind the Policy Statement .....	8
8	Criteria for Commissioning .....	9
9	Patient Pathway .....	9
10	Governance Arrangements .....	9
11	Mechanism for Funding .....	9
12	Audit Requirements .....	9
13	Documents which have informed this Policy .....	9
14	Links to other Policies .....	10
15	Date of Review .....	10
	References .....	10

## 1 Executive Summary

### Policy Statement

NHS England does not routinely commission Bortezomib for the treatment of refractory antibody mediated rejection post kidney transplant.

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.

### 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

The specific questions that were addressed in the review of the research literature were on the clinical effectiveness, safety and cost effectiveness of Bortezomib and the review forms the basis for this policy statement.

Bortezomib is a drug, which is licensed for some indications, that kidney transplant doctors have thought might work to help treat some types of rejection that might occur after a patient receives a kidney transplant. A review of the published evidence from research has failed to find good evidence that the possible benefits from using Bortezomib outweigh any problems such as side effects. This policy states that NHS England will not currently fund this drug for these reasons. If better evidence becomes available then this policy can be reviewed.

## 2 Introduction

Antibody mediated rejection (AMR) is a challenge for the long term survival of grafts in kidney transplantation. It is an important cause of poorly functioning grafts and of graft loss. AMR typically occurs early after transplantation in approximately 5%–7% of patients receiving grafts. Reports suggest that from 12% to 37% of kidney transplant recipients with acute AMR do not respond to treatment and eventually lose their grafts.

The recipient's antibodies may react against a kidney graft and there are a number of existing treatments to try and counter this with varying degrees of evidence to support the presumed benefits over any risks. Early AMR, primarily occurring within the first month after transplantation, has emerged as the next major complication using the current protocols and treatment regimens. The use of the term refractory means that rejection has continued despite the use of the currently recognised treatments.

Some clinicians have started to use Bortezomib for the treatment of difficult episodes of kidney rejection and have requested that this drug is considered for routine commissioning and funding. However, Bortezomib does not have a license or marketing authorization for this clinical indication.

## 3 Definitions

**Renal transplant:** the replacement of a patient's kidneys with a kidney from a donor when the patient's own kidneys have stopped working.

**Antibody mediated rejection (AMR):** After a kidney has been transplanted some patients experience episodes where the body tries to reject the new kidney as it recognizes that it is different. In some cases this happens through the creation of antibodies that act against the kidney. There are treatments to try and suppress this reaction but they do not work in all cases, in which case the AMR is termed refractory.

**Licensed indication for a pharmaceutical drug:** When a drug has sufficiently good research then the company manufacturing it and holding the patent can apply to the appropriate national authority to be given permission to market the drug in line with certain detailed specifications, such as the dose, length of treatment and the types of patients eligible to receive the drug. If a drug is not authorized or licensed then it is considered that there are sufficient uncertainties that the company cannot actively market it for use with patients.

**Good clinical evidence:** It is generally regarded that randomized controlled trials (RCTs) provide the best evidence for a treatment for patients and as to whether any benefits clearly outweigh any risks or problems. In the early stages of drug research clinicians may report their experience with using a drug with certain patients (often termed case series). These studies are regarded as preliminary studies for further more detailed research but on their own are subject to bias.

**Systemic review:** A review of all the clinical research evidence that can be found for a treatment. Systemic means that the review is carried out against certain specified criteria and research questions so that the quality of the available evidence is better understood.

## 4 Aims and Objectives

This policy aims to:

- Specify the clinical circumstances whereby NHS England will commission or not commission Bortezomib for the treatment of refractory AMR

The objectives are to:

- Clarify how the evidence and its quality determines the clinical commissioning position of NHS England for Bortezomib for the treatment of refractory AMR.

The specific questions that were addressed in the review of the research literature were on the clinical effectiveness, safety and cost effectiveness of Bortezomib and the review forms the basis for this policy statement.

## 5 Epidemiology and Needs Assessment

In the financial year 2013/14, 3054 kidney only transplants were performed in the UK. The risk adjusted 5 year graft and patient survival following a deceased donor transplant are 85% and 89% respectively, and 91% and 95% for living donor transplants (NHS Blood and Transplant (NHSBT) Activity Report 2013/14).

Antibody-mediated rejection (AMR) typically occurs early after transplantation in approximately 5% to 7% of recipients. Literature reports suggest that 12% to 37% of kidney transplant recipients with acute AMR do not respond to treatment and eventually lose their grafts. Some of these patients are those who have been considered-potential candidates for Bortezomib.

## 6 Evidence Base

NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the evidence base that was described by the CRG is set out below.

Three studies were found meeting the inclusion criteria of the evidence review. One systematic review (Roberts et al 2012), one controlled trial (Waiser et al. 2012) and one case series (Nigos et al. 2012). No cost-effectiveness studies were found.

- The systematic review by Roberts et al. (with SIGN Level of Evidence 1++) concluded that the evidence supporting the use of Bortezomib is 'very low'. The review included 2 small, non-randomized controlled studies which suggested benefit from Bortezomib (Macaluso et al. 2011, Waiser et al. 2010).

However, these were considered to be of low quality. Furthermore, the effects of dose and regimen on the clinical response were not apparent from the available data.

- The small case series by Nigos et al (2012) (with SIGN Level of Evidence 3) which included 6 patients had a short follow up (mean of 14 months) of which 2 did not respond to treatment. The 4 other patients has stable kidney function.
- A small non randomised trial by Waiser et al (2012) (with SIGN Level of Evidence 2-), assessed clinical effectiveness of Bortezomib (n=10) Vs historical controls (n=9) treated with rituximab. The Bortezomib regimen used was not sufficient to treat all episodes of AMR effectively (only 60% graft survival) however significantly better than the rituximab group (11% graft survival). A potential bias of the study is that it included a less aggressive immunosuppressive treatment regimen than most other studies, which included higher doses of rituximab, higher doses of IVIG, more PPH sessions, the addition of T cell-depleting antibodies and even splenectomy, which could be a reason why graft survival was small in control group.

Overall, the currently available evidence supporting the use of Bortezomib in patients with refractory AMR is limited following kidney transplantation. Further good quality studies are needed to establish its clinical efficacy, safety profile and cost-effectiveness.

## **7 Rationale behind the Policy Statement**

The main conclusion of the evidence review was that the quality of evidence supporting the use of Bortezomib was reported to be 'very low', i.e. limited to uncontrolled studies, including case series and case reports. The uncertainty around the overall benefit means that it is difficult to evaluate the cost effectiveness and at this stage without evidence of benefit then its overall value would be broadly judged as poor.



## **8 Criteria for Commissioning**

Bortezomib will not be routinely funded for the treatment of refractory AMR.

## **9 Patient Pathway**

The existing patient pathway for a patient receiving a renal transplant is described in Section 2.2 of the NHS England Service Specification for Renal Transplant, no: Ao7/S/a, available on the NHS England website.

## **10 Governance Arrangements**

The existing NHS England Service Specification for Renal Transplant, no: Ao7/S/a is available on the NHS England website and on the webpage relating to the Renal Transplant Clinical Reference Group. Specific governance arrangements are not set out for Bortezomib as this commissioning policy specifies that routine funding is not available for the use of Bortezomib.

## **11 Mechanism for Funding**

This commissioning policy specifies that routine funding is not available for the use of Bortezomib. If patients are considered to be clinically exceptional then clinical teams can apply via the individual funding request process of NHS England.

## **12 Audit Requirements**

Not applicable.

## **13 Documents which have informed this Policy**

Evidence review undertaken by NHS England.

## 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 April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

## References

1. NHS England. October 2013. Evidence Review: Eculizumab and Bortezomib for the treatment of refractory antibody mediated rejection post kidney transplant. Reference: NHS England/ A07/P/a.
2. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*. 2012 Oct 27;94(8):775-83.
3. Nigos JG, Arora S, Nath P, Hussain SM, Marcus RJ, Ko TY, Sureshkumar KK. Treatment of antibody-mediated rejection in kidney transplant recipients: a single-center experience with a bortezomib-based regimen. *Exp Clin Transplant*. 2012 Dec;10(6):609-13.
4. Waiser J, Budde K, Schütz M, Liefeldt L, Rudolph B, Schönemann C, Neumayer HH, Lachmann N. Comparison between bortezomib and rituximab in the treatment of antibody-mediated renal allograft rejection. *Nephrol Dial Transplant*. 2012 Mar;27(3):1246-51.
5. Waiser J, Schutz M, Liefeldt L, et al. Treatment of antibody-mediated renal allograft rejection with bortezomib or rituximab (Abstract #1504). *Am J Transplant* 2010; 10(Supp 4): 466.

OFFICIAL