Clinical Priorities Advisory Group summary report

Agenda item	2.1
Date of Meeting	4th June 2025
Title of the Proposition	*Bortezomib for the treatment in acute immune Thrombotic Thrombocytopenic Purpura (TTP) and elective therapy to prevent immune TTP relapse in patients who are refractory or intolerant to rituximab (all ages)*
Unique Reference Number	2103
Programme of Care	Blood and Infection
Clinical Reference Group	Specialised Blood Disorders
Service/treatment status	Highly Specialised Service

Action requested

Support the adoption of the policy proposition

Recommend as a not for routine commissioning policy proposition.

Summary of the proposition:

Bortezomib is not recommended to be available as a routine commissioning treatment option for treatment in acute immune Thrombotic Thrombocytopenic Purpura (TTP) and elective therapy to prevent immune TTP relapse in patients who are refractory or intolerant to rituximab (all ages).

Bortezomib is a proteasome (structures inside cells that break down and recycle proteins that the cell no longer needs) inhibitor that is currently licensed for the treatment of multiple myeloma and mantle cell lymphoma. Bortezomib blocks the proteasomes, this leads to an

accumulation of proteins, causing stress and eventually cell death. It also acts to eliminate CD20-expressing B-cells and plasma cells (which produce the autoantibodies) thus resulting in improved circulating levels of ADAMTS 13. (Patriquin et al., 2016) In the acute setting bortezomib is given alongside PEX, corticosteroids, caplacizumab, and best supportive care.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a not for routine commissioning policy.

If other, please specify below:

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☐
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☐
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒
	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	

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4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).

Evidence Review Summary

In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the clinical effectiveness and safety of bortezomib compared with no bortezomib?

Outcome	**Evidence statement**
Clinical effectiveness	
Critical outcomes	
Mortality **Certainty of evidence:** Very low	Mortality is important to patients because acute immune thrombotic thrombocytopenic purpura (TTP) is a serious, potentially life-threatening condition. In total 1 case series (Patriquin et al. 2016) of 6 people, provided evidence relating to mortality. The study had no comparator treatment and all participants received concomitant rituximab. One person died of cardiac arrest on the 9th day after admission, 5/6 people were alive at follow up (mean 17 months, range 3 to 33 months after discharge). (VERY LOW) This study provided very low certainty evidence that 1 person out of 6 died after bortezomib. No conclusions can be drawn.
Relapse rate **Certainty of evidence:** Not applicable	Relapse rate is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. **No evidence was identified for this outcome.**
Disease response **Certainty of evidence:** Very low	Disease response is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total 1 case series (Patriquin et al. 2016) of 6 people, provided evidence relating to disease response. The study had no comparator treatment and all participants received concomitant rituximab.

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	Resolution of TTP: TTP resolution was reported in 5/6 people. (VERY LOW) ADAMTS13 activity: at time of discharge ADAMTS13 activity ranged from 75 to 89% (Case 1: 87%; Case 2: 89%; Case 3: died; Case 4: 83%; Case 5: 83%; Case 6: 75%). (VERY LOW) At mean 17 months follow up after discharge (range 3 to 33 months) ADAMTS13 activity had increased in 5/6 cases ranging from 65 to 119% (Case 1: 116%, 33 months; Case 2: 119%, 12 months; Case 3: died; Case 4: 106%, 19 months; Case 5: 65%, 18 months; Case 6: 87%, 3 months). (VERY LOW) Time from first bortezomib dose to platelet normalisation (days): 3 to 29 days (Case 1: 6; Case 2: 3; Case 3: died; Case 4: 12; Case 5: 29; Case 6: 21 days). (VERY LOW) This study provided very low certainty evidence on disease response (ADAMTS13 activity and platelet normalisation) after bortezomib. All people who survived had an ADAMTS13 activity greater than 10% at discharge and follow up and all had platelet normalisation within 29 days. However, because there was no comparator and rituximab was given concomitantly in 5/6 people, no conclusions can be drawn.
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life is an important outcome to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. **No evidence was identified for this outcome.**
Functional measures **Certainty of evidence:** Very low	These outcome measures are important to patients as they facilitate enablement, independence and active participation. In total 1 case series (Patriquin et al. 2016) of 6 people, provided evidence relating to functional measures. The study had no comparator treatment and all participants received concomitant rituximab. Functional measures reported: Neurological resolution reported in 2/6 people. Transient atrial fibrillation with normal echo reported in 1/6 people. Partial blindness and hearing loss in 1/6 people. Confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest in the person who died. (VERY LOW) This case series provides very low certainty evidence on the effect of bortezomib on functional measures. The authors reported a range of descriptive functional measures. However, because there was no

	comparator and rituximab was given concomitantly in 5/6 people, no conclusions can be drawn.
Hospitalisation **Certainty of evidence:** Not applicable	Hospitalisation is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very low	Safety outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. One case series (n=6) provided evidence relating to adverse events. The study had no comparator treatment and all participants received concomitant rituximab. Of the 5/6 people who survived, no adverse events were reported. (VERY LOW) This case series provides very low certainty evidence on the safety of bortezomib. The authors reported that there were no adverse events in the 5/6 people who survived.

In people diagnosed with immune TTP who are refractory or intolerant to rituximab or obinutuzumab, what is the clinical effectiveness and safety of bortezomib treatment to prevent acute relapse compared with no bortezomib?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Relapse rate **Certainty of evidence:** Not applicable	This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. **No evidence was identified for this outcome.**
Disease response **Certainty of evidence:** Not applicable	This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. **No evidence was identified for this outcome.**
Hospitalisation	This outcome is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their

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Certainty of evidence: Not applicable	treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. **No evidence was identified for this outcome**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	This is an important outcome to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform patient centred shared decision making and health policy. **No evidence was identified for this outcome.**
Functional measures **Certainty of evidence:** Not applicable	This outcome measure is important to patients as they facilitate enablement, independence, and active participation. **No evidence was identified for this outcome.**
Mortality **Certainty of evidence:** Not applicable	This is important because acute immune TTP is a serious, potentially life-threatening condition. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Not applicable	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. **No evidence was identified for this outcome.**

In people with immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the cost effectiveness of bortezomib compared with no bortezomib?

Outcome	Evidence statement
Cost effectiveness	**Acute immune TTP** **No evidence was identified for this outcome.**
	Prevention of immune TTP relapse **No evidence was identified for this outcome.**

In people diagnosed with immune TTP who are refractory or intolerant to rituximab or obinutuzumab, what is the clinical effectiveness and safety of bortezomib treatment to prevent acute relapse compared with no bortezomib?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Relapse rate **Certainty of evidence:** Not applicable	This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. **No evidence was identified for this outcome.**
Disease response **Certainty of evidence:** Not applicable	This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:** Not applicable	This outcome is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. **No evidence was identified for this outcome**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	This is an important outcome to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform patient centred shared decision making and health policy. **No evidence was identified for this outcome.**
Functional measures **Certainty of evidence:** Not applicable	This outcome measure is important to patients as they facilitate enablement, independence, and active participation. **No evidence was identified for this outcome.**
Mortality **Certainty of evidence:**	This is important because acute immune TTP is a serious, potentially life-threatening condition. **No evidence was identified for this outcome.**

Not applicable	
Safety	
Adverse events **Certainty of evidence:** Not applicable	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. **No evidence was identified for this outcome.**

In people diagnosed with immune TTP who are refractory or intolerant to rituximab or obinutuzumab what is the cost effectiveness of bortezomib treatment to prevent acute relapse compared with no bortezomib?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for this outcome.**

From the evidence selected, are there any subgroups of patients that may benefit from bortezomib treatment to prevent acute relapse more than the wider population of interest?

Outcome	Evidence statement
Subgroups of patients	**No evidence was identified for this outcome.**

From the evidence selected, at what ADAMTS 13 level was preventative treatment started?

Outcome	Evidence statement
Criteria to define haematological relapse	**No evidence was identified for this subgroup of patients.**

From the evidence selected, what dose regimens of bortezomib treatment to prevent acute relapse were used?

Outcome	Evidence statement
Dose regimes	No evidence was identified for this outcome.

Patient Impact assessment

The condition has the following impacts on the patient's everyday life:

- **mobility:** patients can have severe problems in walking about and other disabilities, especially if they have suffered a stroke or seizures.
- **ability to provide self-care:** patients can have moderate-severe problems in washing or dressing and cooking as well as attending hospital and doctors' appointments on their own.
- **undertaking usual activities:** patients can have severe problems in doing their usual activities, including going to work or making a living. Fatigue, memory loss, concentration problems and aphasia and symptoms of PTSD can make returning to their 'old life' challenging and often impossible.
- **experience of pain/discomfort:** patients can have moderate pain or discomfort, particularly in joints. Patients are frequently diagnosed with fibromyalgia.
- **experience of anxiety/depression:** patients can be severely - extremely anxious or depressed. PTSD can be a feature among patients due to the sudden and unexpected onset of TTP and the seriousness of the condition.

Further details of impact upon patients:

Following an episode of acute immune TTP, patients are often left with long-lasting sequelae. These include life changing fatigue as well as memory and concentration difficulties and seizures. All patients have some degree of global brain injury and are often unable to return to full time work. Similarly, adolescent patients can face difficulty with schooling.

Many people suffer with anxiety as a result of the after-effects of an acute episode of immune TTP as well as the anxiety of further relapse. Additionally, patients can suffer recurrent transient ischaemic attacks and fits following acute immune TTP. This can result in patients being unable to drive which can massively impact their independence. Some patients experience extreme anxiety and depression when their ADAMTS13 levels become low.

Patients with acute or refractory immune TTP are usually treated with rituximab, which is often effective. However, a proportion of these patients are refractory or intolerant to rituximab, leaving them with limited treatment options. Given that these patients have already failed to respond to other standard therapies and are at high risk of relapsing, this is a particular concern since they will return to life- or organ-threatening disease. To treat this, they will often be treated with immune suppressing drugs, such as mycophenolate mofetil (MMF) or cyclosporin. This can increase the risk of fatal infections in the short term, and long-term use may increase the risk of cancer, cause renal impairment, and hypertension. Patients who fail to achieve immunological remission are also more likely to be exposed to multiple doses of steroids, often at high doses. Repeated steroid use can lead to long term side effects such as weight gain, osteoporosis, depression, infection, and early cardiovascular disease.

Further details of impact upon carers:

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Immune TTP can lead to a high burden on the carer to help with many self-care tasks, which may be difficult or impossible for the person during an acute relapse. Families and/or carers may have to help with tasks such as bathing, cleaning teeth, dressing and undressing, cooking and preparing meals, ironing, cleaning the house, getting out and about or help using mobility aids. There is a significant burden of anxiety and depression from the carer point of view as well as substantial concern regarding family planning. Additionally, immune TTP places a significant financial burden on the family of those affected due to the patient themselves being often unable to work as well as a high dependency on carer support. The impact on carers due to the fear of relapse (by both patient and carer) should not be underestimated.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	There is insufficient evidence to support the treatment of TTP with bortezomib. Consequently, there is no change to the current treatment pathway, as it is not currently commissioned and therefore no impact on patients.
13Q Assessment	
PPVAG outcome	Public consultation
Were PPVAG assured of the level of stakeholder testing?	Yes. The Lead Commissioner for the policy proposition from the Highly Specialised Services team presented the 13Q for this clinical policy proposition. It was recommended by the Programme of Care that this proposition undergoes a 30-day public consultation. After clarification on this, the PPVAG assured this recommendation.
Rare Disease Advisory Group	
Yes. Discussed at RDAG on 29th April 2025. Committee members were supportive of this policy proposition.	
Pharmaceutical	
Yes	

The clinical commissioning policy proposition does not recommend use of bortezomib in treatment of acute immune Thrombotic Thrombocytopenic Purpura (TTP) and elective therapy to prevent immune TTP relapse in patients who are refractory or intolerant to rituximab (all ages). Use in this indication is not within the product's marketing authorisation, so any use would be off-label. Bortezomib is on the NHS Payment Scheme Annex A, that is, it is ahigh-cost drug.

National Programme of Care

Blood and Infection Programme of Care

The policy proposition was discussed by the PoC assurance group on 25th July 2023 and the NRC position was supported.

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