CLINICAL PRIORITIES ADVISORY GROUP
6th September 2023

Agenda Item No	2.4
National Programme	Blood and Infection
Clinical Reference Group	Specialised Bleeding Disorders
URN	2255

Title
Obinutuzumab elective therapy to prevent immune Thrombotic Thrombocytopenic Purpura (TTP) relapse in patients who are refractory or intolerant to rituximab (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
TTP is a rare, potentially life-threatening condition that involves formation of blood clots in the small blood vessels in the body due to a shortage of an enzyme known as ADAMTS13. ADAMTS13 is responsible for breaking down von Willebrand Factor, which in turn is responsible for blood clot formation. This increase in blood clots leads to a reduction in the number of platelets in the blood vessels which leads to increased bleeding and a reduction in blood flow to different parts of the body. This interruption in blood flow to parts of the body can lead to organ damage. Any organ could be affected by this, but it generally affects the brain leading to strokes, digestive tract, heart and kidneys. Without treatment, the mortality in acute TTP is over 90% and relapse rate is approximately 30-50% although this figure is reducing with the use of rituximab in the acute presentation. TTP can affect people of all ages though it is very rare in children. The median age at presentation is 30-40 years old. It tends to affect women more than men in a 2:1 ratio. The incidence of new immune TTP is between 1-3 per million per year. Historical data from the TTP registry shows that 30% of patients treated with rituximab will relapse over 10 years, with a proportion relapsing on multiple occasions. At least 8-10% of these relapsing patients will be refractory or intolerant to rituximab. This would currently equate to roughly 10-30 patients a year in England. The current national protocol is to use plasma exchange, known as PEX, in acute cases. Plasma exchange replaces blood plasma with new plasma fluid. Following this,

patients are given immunosuppression initially with high dose steroids and rituximab to switch off the immune system response causing the increased clotting in the blood. Rituximab is a monoclonal antibody that targets the CD20 molecule, improving circulating levels of ADAMTS13.

Rituximab is also used in the outpatient setting to prevent acute TTP relapse when a patient's ADAMTS13 levels fall too low. The median time following an acute episode is 2-2.5 years, but there is a second 'peak' 7-9 years after initial therapy. Obinutuzumab is a humanised CD20 monoclonal antibody, currently licenced for the treatment of chronic lymphocytic leukaemia and follicular lymphoma in adults. Despite having the same mechanism as rituximab, because obinutuzumab is humanised, patients are less likely to develop tolerance or antibodies to it.

For those patients who are intolerant or refractory to rituximab, obinutuzumab is an alternative treatment option to prevent acute disease relapse in patients whose ADAMTS13 levels are falling.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning proposition.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The 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.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Outcome 1 **Relapse rate** **Certainty of evidence:** Very low	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. In total, 1 case series (Doyle et al 2022) of 15 people, provided very low certainty evidence relating to relapse rate. The study had no comparator treatment and 8 people received obinutuzumab. Of the 8 people treated with obinutuzumab, 2 people were treated for acute (clinical) relapse (outside the PICO population) and 6 people were treated for ADAMTS13 relapses. The median follow-up time until ADAMTS13 normalised was 7.7 months in the 8 people taking obinutuzumab. No relapses were reported in this time. The median relapse-free survival was 15.4 months. One participant was reported to have had a relapse after obinutuzumab treatment. **(VERY LOW)** **This study provided very low certainty evidence that ADAMTS13 normalises after a median time of 7.7 months in people with relapsed immune TTP treated with obinutuzumab. No relapses were reported in this time in the study, but 1 person relapsed after a median 15.4 months, suggesting any benefits seen with obinutuzumab might not be maintained longer-term. However, no firm conclusions can be drawn from an open-label, retrospective study with no comparator.**
Outcome 2 **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 (Doyle et al 2022) of 15 people provided non-comparative evidence relating to disease response. This outcome was reported for a mixed population treated with either ofatumumab or obinutuzumab. The majority of treatment episodes were for ADAMTS13 relapse (21/26, 81%). The rest were for acute (clinical) relapse (4/26, 15%) and de novo acute immune TPP (1/26, 4%), which are outside of the PICO population.

	Of 26 treatment episodes with obinutuzumab or ofatumumab, 24 (92%) resulted in complete remission (ADAMTS13 activity levels at least 60 iu/dl) and the other 2 (8%) resulted in partial remission (ADAMTS13 activity 20–59 iu/dl). **(VERY LOW)** The median time to complete remission was 15 days (IQR 11.5–32.5 days). **(VERY LOW)** **This study provided very low certainty evidence suggesting that treatment with obinutuzumab or ofatumumab can result in complete or partial remission in people with ADAMTS13 relapses. The median time to complete remission was around 15 days. There was no comparator and outcomes were not reported separately for each intervention, so no conclusions can be drawn.**
Outcome 3 **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	
Outcome 4 **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.**
Safety	
Outcome 5 **Adverse events** **Certainty of evidence:** Very low	Adverse events 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, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. One case series (n=15) provided evidence relating to adverse events. The study had no comparator treatment and the participants received either ofatumumab or obinutuzumab. The majority of treatment episodes were for ADAMTS13 relapse (21/26, 81%). The rest were for acute (clinical) relapse (4/26, 15%) and de novo acute immune TPP (1/26, 4%), which are outside of the PICO population. Two participants had infections needing treatment (COVID-19 and UTI) and 2 participants had infusion-

	related reactions. No participants died or had serum sickness. **(VERY LOW)** **Four of 15 participants had 4 adverse events during 26 treatment episodes. Two participants had infections needing treatment (COVID-19 and UTI) and 2 participants had infusion-related reactions. No participants died or had serum sickness. This case series reported little information on adverse effects, and it provides very low certainty evidence on the safety of obinutuzumab. Four adverse events were reported during 26 treatments episodes, and it is not known whether these were in people taking obinutuzumab or ofatumumab. Therefore, no conclusions can be drawn about the safety of obinutuzumab.**
Abbreviations TTP, Thrombotic thrombocytopenic purpura; IQR, Interquartile range; UTI urinary tract infection	

In the Population what is the cost effectiveness of the Intervention compared with Comparator?

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 the intervention more than the wider population of interest?

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

Patient Impact Summary
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 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 TTP as well as the anxiety of further relapse. Additionally, patients can suffer recurrent transient ischaemic attacks and fits following acute 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 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 worry since they will return to life- or organ-threatening disease. To treat this, they will often be given high dose steroids to suppress disease progression. Long term steroid use leads to long term side effects such as weight gain, osteoporosis, depression, infection, and early cardiovascular disease.

Further details of impact upon carers:

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, 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 from review by Rare Disease Advisory Group

RDAG was supportive overall but highlighted the need for ongoing collection and review of outcome data for the treatment particularly for post-pubescent children. RDAG also encourages formal publication of this data in order to improve the evidence base.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends obinutuzumab for adults as an elective therapy to prevent immune TTP relapse in patients who are refractory or intolerant to rituximab. The recommendation is outside obinutuzumab' s marketing authorisation, so use is off-label. Obinutuzumab is excluded from tariff. Post-pubescent children will be able to access obinutuzumab under the Medicines for Children policy.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood and Infection Programme of Care on 23rd May 2023