NICE National Institute for Health and Care Excellence

Highly Specialised Technologies (HST) criteria checklist

Iptacopan for treating complement 3 glomerulopathy ID6283

Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see Appendix 1: highly specialised technologies of the NICE-wide topic prioritisation manual.

Met	There is clear and strong evidence that the criterion is met
Not met	There is some, but not enough clear evidence that the criterion is met or There is no evidence or limited evidence that the criterion is met.

MA wording: [redacted]

Number	Criterion	Description of how the technology meets the criteria	Does the technology meet the criteria?
1.	The disease is very rare defined by a prevalence of lower than 1:50,000 in England, or around 1,100 people.	**Pre-consultation:** • Prevalence estimates between 0.25 per 50,000 to 12.5 per 50,000 • Company PharmaScan entry lists UK patient population range as 'Between 1 per 50,000 and 25 per 100,000' How the prevalence estimates were calculated:	Met

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		• A 2014 retrospective study identified patients from a centre in London and a centre in Dublin that had pathological criteria demonstrating the presence of C3 glomerulopathy. The estimated incidence at the London centre was 1 case per million population, and at the Dublin centre was 2 cases per million population (Medjeral-Thomas, 2014)
		  ○ The company used these data and an assumed median disease duration of 20 years to derive a prevalence estimate of 0.2 per 10,000 people.
		
		• A 2019 review listed 5 studies with epidemiology estimates, including the study (Medjeral-Thomas) above. Applying the formula below, the range of prevalence estimates was from 0.05 to 1.4 per 10,000 population (0.25 to 7 per 50,000). For the UK study listed above, the prevalence estimate was 1.3 per 10,000, or 6.5 per 50,000 (Smith, 2019)
		  ○ Prevalence formula: (n cases/n referral population) × (population average life expectancy – median or mean age of case patients)/n years of data collection.
		  ▪ This formula may overestimate prevalence if C3G affects mortality risk.
		
		Company response summary:
		
		• Medjeral-Thomas, 2014 is a retrospective review that may overestimate prevalence. Multiple issues with Smith, 2019, including cannot verify incidence estimates from included studies, formula does not consider mortality risk.
		• National Organisation for Rare Disorders (NORD) estimate 0.1 to 0.15 per 50,000 (US based)	

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		• National Registry of Rare Kidney Diseases (RaDaR) data from 109 renal centres across the UK. June 2024 data from 1,226 patients with membroproliferative glomerulonephritis (MPGN) includes a subset of people with C3G and people with inmmune-complex mediated MPGN ○ To estimate prevalence of C3G group company uses 2023 analysis of 287 with an exact diagnosis recorded 47% had C3G and 53% had IC-MPGN. Applied split to whole population taking account of 157 deaths prior to July 2022. Estimated prevalence as 502 UK overall, 424 patients for England (0.37 per 50,000 people) **Prioritisation board conclusion:** • On balance, more likely met than unmet. Company's initial estimate on the cut-off and some estimates above 1:50,000. However, RaDaR from a larger sample of UK centres (than Medjeral-Thomas 2014). Assumptions on the proportion of people with C3G from this mixed cohort add uncertainty on exact prevalence.	
2.	Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications	**Pre-consultation:** • Adult population in England was approximately 45.7 million in mid-2023 (ONS). Using the pre-consultation prevalence estimates above, approximately 230 to 11,000 people with C3G. • Iptacopan is indicated for paroxysmal nocturnal haemoglobinuria and has positive NICE guidance (TA1000). The budget impact test for this estimates ~220 eligible patients. • Iptacopan is also in phase II/III clinical development for the following indications which would add a significant eligible population	Met

Number	Criterion	Description of how the technology meets the criteria	Does the technology meet the criteria?
		○ Other kidney diseases such as Lupus Nephritis and Primary IgA Nephropathy ○ Atypical Hemolytic Uremic Syndrome ○ Anti-Neutrophil Cytoplasm Antibodies (ANCA) Associated Vasculitis ○ Age-Related Macular Degeneration ○ Autoimmune Benign Hematological Disorders **<u>Company response summary:</u>** • Using RaDaR dataset, 424 patients with C3G in England. • Applying following exclusions: ○ <18 years old: -21% (licence expected to cover adults only) ○ Proteinuria <1g/day: -38% ○ With kidney failure: -37% • This leaves 131 eligible patients, plus 48 whose C3G is post-transplant recurrent. 179 total. • Only other NICE approval is for paroxysmal nocturnal haemoglobinuria, NICE resource impact statement estimates 117 patients. • Total eligible patients across all indications: 296 **<u>Prioritisation board conclusion:</u>** • Reasonable for company to use updated value for PNH based on resource impact statement. • If iptacopan delays progression to kidney failure would expect eligible population size to increase as more people start treatment earlier in the condition's course.	

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		• Potential for post-pubescent people <18 years to meet Commissioning Medicines for Children in Specialised Services (2024) criterion, which may increase the population who would have this treatment if recommended by NICE. • Overall, accept estimates of prevalence based on RaDaR, likely this criterion is met.	
3.	The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life	**Pre-consultation:** • Unclear whether C3G is associated with significant excess mortality. • Company indicates that median disease duration is 20 years, which would not suggest significant excess mortality. • 10 years after diagnosis, approximately 50% will progress to kidney failure and require dialysis or transplant to stay alive. • Recurrence after transplant occurs in more than 50%. • Having ESRD is associated with poorer quality of life. People may have additional symptoms resulting from deposits in other tissues to the kidney. **Company response:** • [redacted] • Approximately 50% of patients progressing to kidney failure within 10 years of diagnosis.	Met

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		• Given the young age at diagnosis (21 to 23), this results in people being reliant on chronic dialysis from a young age, or requiring a kidney transplant.
		• Kidney transplant is not curative in C3G, high rate of post-transplant recurrence (55 to 85%), requiring further transplant or dialysis.
		• Chronic kidney disease is associated with cardiovascular disease and increased risk of mortality. For C3G, a substantial loss in life years can be assumed given the affected people's young age:
		  ○ UK cohort standardised mortality ratio of 36.4 in CKD patients aged 16 to 49 years.3
		  ○ US study estimated that a 20-year-old with CKD loses on average 15.6 life years compared with a 20-year-old without CKD, while a 70-year-old with CKD would on average lose 3.9 life years.
		• Quality of life is impacted by symptoms of C3G as well as anxiety and depression associated with uncertainty around future disease progression.
		• Note also the impact on quality of life of co-morbid cardiovascular disease, acquired partial lipodystrophy and ocular complications such as retinal drusen. People with C3G may also experience periodic episodes of gout, leading to joint pain.
		
		Prioritisation board conclusion:
		• Having CKD shortens life and reduces quality of life. There may be a greater relative reduction in life expectancy for people who have this condition from a younger age. Overall, more likely met than unmet.	

Number	Criterion	Description of how the technology meets the criteria	Does the technology meet the criteria?
4.	There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.	**Pre-consultation:** • Iptacopan intended to [redacted] and is not curative – unclear if this meets the threshold of significant additional benefit. • Not clear whether iptacopan generates additional benefits over eculizumab in the post-transplant recurrent setting. • Usual treatment includes steroids, immunosuppressants, and hypertensive treatments (ACE inhibitors/ARBs). If a person has end stage kidney disease they will need dialysis or a kidney transplant. More than 50% of people will have disease recurrence after kidney transplant. • NHS England commissions eculizumab for post-transplant recurrent patients (see policy). • Early results from trials show benefit over placebo in proteinuria endpoint which the study authors say may suggest that iptacopan could slow disease progression. **Company response summary:** [redacted] • None of the currently used treatments – including eculizumab – target the underlying cause of C3G. • Iptacopan is an oral, first-in-class Factor B inhibitor which selectively inhibits the alternative pathway of the complement system, and thus addresses the underlying cause of C3G.	Not met

Number	Criterion	Description of how the technology meets the criteria	Does the technology meet the criteria?
		• In clinical trials, iptacopan demonstrated reduction in proteinuria and stabilisation of kidney function. • The high unmet need and clinicians' expectation of iptacopan providing significant additional benefit in C3G are evidenced by compassionate use requests and enrolment of UK patients in iptacopan clinical trials. • The company (and NHS England in scope consultation comments) noted that only a small proportion of people whose C3G has reoccurred after kidney transplant would be eligible for eculizumab. **<u>Prioritisation board conclusion:</u>** • Most recent results from trial indicate iptacopan patients had a sustained reduction in proteinuria and decreased slope of kidney function decline. Non-surrogate outcomes not available. When a person's condition progresses to kidney failure that person will need dialysis/kidney transplant. Both dialysis and kidney transplants have resource constraints and stakeholders further note that black people and people of Asian family backgrounds have longer waiting times for kidney transplant. No satisfactory treatment options in earlier stages of kidney disease before kidney failure. Satisfactory treatment would prevent/significantly reduce the need for dialysis or kidney transplant, but unclear if iptacopan will have a significant benefit as slows rather than stops progression.	