National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Sanofi	The remit wording is accurate. Please see below for alternative wording for remit: 'To appraise the clinical and cost effectiveness of caplacizumab within its marketing authorisation for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura.'	Thank you for your comments. We have amended the remit to be more precisely in line with the wording in the marketing authorisation. The remit is now: To appraise the clinical and cost effectiveness of caplacizumab within its marketing authorisation for treating adults experiencing an episode of acquired thrombotic

Section	Consultee/ Commentator	Comments [sic]	Action
			thrombocytopenic purpura.
	Genetic Alliance UK	This matches the standard wording	Thank you for your comments. We have amended the remit to be more precisely in line with the wording in the marketing authorisation. The remit is now: To appraise the clinical and cost effectiveness of caplacizumab within its marketing authorisation for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura.
	TTP Network	The draft remit does not identify that Caplacizumab, under the name 'Cablivi' It is considered an orphan drug by the European Medicines Agency - https://www.ema.europa.eu/en/medicines/human/EPAR/cablivi. The draft remit should, from a TTPNetwork perspective, therefore include reference to the UK Strategy for Rare Diseases (2013) and the updated implementation plan (2019). This seems an omission as both policy documents refer to orphan drugs and the role of the EMA. Furthermore, the	Thank you for your comments. The remit is intended to provide a brief overview of what the scope will cover and the appraisal

Section	Consultee/ Commentator	Comments [sic]	Action
		MHRA has a role on this group and therefore we take that as meaning that the UK supports the EMA's decision making. https://www.gov.uk/government/publications/rare-diseases-strategy https://www.gov.uk/government/publications/uk-strategy-for-rare-diseases-2019-update-to-the-implementation-plan-for-england	objective. The appraisal process will consider the specific details of the topic. We have amended the remit to be more precisely in line with the wording in the marketing authorisation. The remit is now: To appraise the clinical and cost effectiveness of caplacizumab within its marketing authorisation for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura.
Timing Issues	Sanofi	On the 28th June 2018, caplacizumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), with the recommendation of the granting of marketing authorisation (MA) for the treatment of aTTP. Caplacizumab received a MA valid throughout the European Union on 30th August 2018. A specialist service provision is in progress with NHS England (NHSE).	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	Given, compared to comparators, the effectiveness demonstrated in clinical trials of the intervention for those with a condition that can result in death, it is urgent that it is appraised in a timely fashion.	Thank you for your comments.
	TTP Network	Caplacizumab is licenced and approved for use in the USA and parts of mainland Europe. As a European country the UK is not able to offer the same treatment as its neighbour countries. This inequity would seem counter to the relatively positive way the UK Strategy for Rare Diseases puts on treatment for rare diseases; the support for research in this area; and its recognition of orphan drugs. https://www.ema.europa.eu/en/medicines/human/EPAR/cablivi https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approved-caplacizumab-yhdp	Thank you for your comments.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi	Background information does not adequately convey the nature of the disease. aTTP is associated with acute life-threatening episodes, and long-term sequelae for survivors of acute events. *Thrombotic thrombocytopenic purpura (TTP) is a rare, thrombotic microangiopathy which can present as an acute life-threatening disorder requiring prompt diagnosis, early referral and effective immediate management. TTP results from systemic microvascular thrombosis associated with to profound thrombocytopenia, haemolytic anaemia, and*	Thank you for your comments. We have amended the background section of the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		organ failure of varying severity. The diagnosis of TTP should be treated as a medical emergency. *Acquired or immune-mediated TTP (aTTP) is caused by a severe immune-mediated deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) due to the presence of anti-ADAMTS13 autoantibodies.* *This deficiency in ADAMTS13 activity leads to an accumulation of ultra large von Willebrand factor multimers (ULvWF) allowing unrestrained adhesion of von Willebrand factor (vWF) multimers to platelets and formation of platelet-rich microthrombi in small blood vessels with thrombocytopenia. Systemic microthrombi, by occluding vessels, results in microangiopathic haemolytic anaemia, tissue ischemia and organ dysfunction (typically the brain, the heart, and kidneys). If left untreated, aTTP is invariably fatal. In patients who recover from an aTTP episode report cognitive deficits, depression, arterial hypertension, autoimmune diseases, and a shortened life expectancy.*	
	Genetic Alliance UK	Some sources estimate incidence of TTP to range as high as 11 cases per million (https://www.ttpnetwork.org.uk/about-ttp/). Prevalence of TTP in France has been estimated to be 13 cases per million (www.bit.ly/2Ygs2OJ), extrapolated to the UK that would give a total UK population of approximately 819.	Thank you for your comments. We have amended the background section of the scope.
	TTP Network	The background information does not fully explain the extreme seriousness of TTP. Without prompt treatment – death is very likely. TTP patients report ongoing issues such as poor cognitive function, Aphasia, memory loss, depression & anxiety following TTP. In many cases there are effects of Strokes and organ damage. These are long term effects. The background information is weak.	Thank you for your comments. We have amended the background section of the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	Sanofi	Only the first dose of caplacizumab (10mg) is administered intravenously (IV). Initiation is via IV injection of caplacizumab (10mg) as a loading dose prior to plasma exchange (PEX), followed by daily subcutaneous (SC) administration of caplacizumab (10mg) after completion of each PEX for the duration of daily PEX treatment. Maintenance is via daily SC injection of caplacizumab (10mg) for 30 days after stopping daily PEX treatment.	Thank you for your comments. This section has been updated.
	Genetic Alliance UK	-	-
	TTP Network	Nothing to add	Thank you for your response.
Population	Sanofi	The population is defined appropriately.	Thank you for your response.
	Genetic Alliance UK	-	-
	TTP Network	There is some evidence to show greater incidence of TTP among the black African Caribbean community. It also seems that women are more affected. NICE should however recognise that aTTP is a rare disease and attempting to investigate specific population groups, considering the remit, may not add value.	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	Sanofi	Yes, plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab is the standard treatment currently used in the NHS. The draft scope refers to a sub-group with severe refractory aTTP and that the current standard of care in this group includes a combination of one or more of: Plasma exchange therapy (with or without spun apheresis, steroids, rituximab, splenectomy, vincristine or immunosuppression e.g. cyclophosphamide) without caplacizumab. Refractory disease cannot be identified before treatment initiation, and there is no clinical evidence supporting this population. These treatments listed as comparators (vincristine and cyclophosphamide) are very rarely used and splenectomy is no longer advised so are not reflective of current practice (Barbour et al. Nephrol Dial Transplant (2012) 27:2673-85). This is also supported by current clinical expert opinion. As such, 'Plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab' should be the comparator considered for all patients with aTTP.	Thank you for your comments. NICE considers the subgroup 'severe refractory acquired TTP' to be an appropriate subgroup and should be included if evidence allows. Limitations of the subgroup analyses will be taken into account in the committee's decision making. No action required.
	Genetic Alliance UK	-	-
	TTP Network	A question is included about established clinical practice in the NHS for episodes of aTTP. The TTPNetwork would steer NICE to the draft specification and its detail therein, published as part of a consultation by NHSE - https://www.engage.england.nhs.uk/consultation/thrombocytopenic-purpura/user_uploads/thrombotic-thrombocytopenic-purpura-service-specification.pdf	Thank you for your comments. NICE considers the subgroup 'severe refractory acquired TTP' to be an appropriate subgroup and should be included if evidence

Section	Consultee/ Commentator	Comments [sic]	Action
		In terms of comparators and related research then TTPNetwork would encourage NICE to consider the full research published in the New England Journal of Medicine – for abstract see: https://www.nejm.org/doi/full/10.1056/NEJMoa1806311 NICE might also want to consider this paper published by Clinicians working in the field of treating aTTP: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12718	allows. Limitations of the subgroup analyses will be taken into account in the company submission and the committee's decision making. No action required.
Outcomes	Sanofi	Yes. In addition to the outcomes listed in the scope, neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode are commonly cited.	Thank you for your comments. The outcomes section has been updated to include: Neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode
	Genetic Alliance UK	-	-
	TTP Network	There are documented long term effects of TTP. Use of Caplacizumab will reduce hospital stays and reduce exposure to donor blood products. Extended stay in hospital can be a risk in terms of infection, reduced mobility, and isolation (and related health implications). The Hercules trial includes information on health care utilisation and shows reductions in terms of reduced plasma exchange procedures; volume of plasma and in patient stay.	Thank you for your comments. The outcomes section has been updated to include:

Section	Consultee/ Commentator	Comments [sic]	Action
			Neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode
Economic analysis	Sanofi	The economic analysis will follow the NICE reference case, with a lifetime time horizon.	Thank you for your comments
	Genetic Alliance UK	-	-
	TTP Network	TTPNetwork would like to see NICE liaising with NHS clinicians/researchers involved in the Hercules Trial on this aspect to enable NICE to better understand the quality of life impact and any follow up information available.	Thank you for your comments. The company is responsible for providing the economic analyses, and clinical experts will be invited to be involved in the process.
Equality and Diversity	Sanofi	aTTP is more prevalent in females and in people of Afro-Caribbean descent. Patients with an active HIV infection are at a greater risk of developing aTTP than the general population.	The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	We understand that that the condition affects women more than it does men on a scale of 3:2.	The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	TTP Network	aTTP is a rare disease and does appear to affect more women than men, which could have broader impact on families. TTP has a disproportionate impact on women, and women of childbearing age. When spending long periods in hospital, the impact on families is profound. There is also an impact on earnings and earning potential as many patients do not return to full time work, or work in the same capacity as before diagnosis. As mentioned above the Black African Caribbean community are adversely affected by TTP. Patients who are cognitively impaired or less able to express themselves are less likely to push for/demand follow up care and therefore are more likely to relapse needing hospital care (rather than receiving rituximab as a preventative medicine).	The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.

Section	Consultee/ Commentator	Comments [sic]	Action
		Patients with mobility issues may find it more difficult to attend follow up appointments and will be therefore more likely to miss out on opportunities to receive preventative treatment.	
Other considerations	Sanofi	The scope refers to a subgroup analysis of people with severe refractory aTTP, if evidence allows. The sub-group of patients with severe refractory aTTP has no clinical evidence specific to this population and refractoriness cannot be clinically defined at the point at which caplacizumab would be initiated. Clinical expert opinion suggests that each aTTP episode is treated individually and the same treatment protocol applied. As such there is no evidence to support considering this as a subgroup. Furthermore, there are no other subgroups of people in whom caplacizumab is expected to be more clinically effective or cost effective.	Thank you for your comments. NICE considers the subgroup 'severe refractory acquired TTP' to be an appropriate subgroup and should be included if evidence allows. Limitations of the subgroup analyses will be taken into account in the committee's decision making. No action required..
	Genetic Alliance UK	-	-
	TTP Network	Nothing to add.	Thank you for your response.
Innovation	Sanofi	The current standard of care treatment for aTTP (PEX and immunosuppression) does not directly address the pathophysiological platelet adhesion leading to the formation of microthrombi. Thus, there remains a significant unmet medical need for rapid-onset therapies directly inhibiting the formation of microthrombi and tissue ischemia. There is also slow onset of	Thank you for your comments. Innovation will be considered as part of the appraisal process.

Section	Consultee/ Commentator	Comments [sic]	Action
		efficacy with current standard of care, and response to PEX cannot be predicted when treatment is initiated. In an acute disease setting, where immediate and effective intervention may be critical for survival and prevention of short-term and long-term damage, a rapidly acting medicine that offers immediate protection is needed. Caplacizumab is innovative in being the first licensed treatment specifically for aTTP. It targets the A1 domain of von Willebrand factor, directly inhibiting platelet aggregation and microvascular clotting. In early clinical studies this inhibition of platelet aggregation was observed almost immediately after administration of the loading dose. Caplacizumab is the first licensed nanobody in any indication; this technology is derived from the discovery of camelid (llamas and related species) heavy-chain only antibodies. Caplacizumab has shown reduction in mortality associated with acute events – no patient in the intervention arm of either study died of TTP during the treatment period, in contrast to placebo. No patient treated with caplacizumab developed refractory TTP. Exacerbations (early recurrences of acute TTP) were seen much less frequently in the treated group versus the placebo group. Long term consequences of vascular occlusion are reported, particularly cerebrovascular. Length of time in a state with occlusions is likely to impact on severity of long-term sequelae, although evidence is currently sparse, it should be considered.	

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	In its ability to greater supplement existing therapies by reducing blood clots and so episodes of the condition it represents an innovation in its treatment.	Thank you for your comments. Innovation will be considered as part of the appraisal process.
	TTP Network	TTPNetwork considers this technology both innovative and a breakthrough which as part of the current standard care has proven to make a significant impact on treating aTTP. TTPNetwork has had full access to the NEJM paper and the results reported appear to provide substantive evidence that this technology has: - significant clinical benefits in terms of reducing risk of adverse thrombotic episodes - significant clinical impact on platelet count - significant reduced plasma exchange and volume - significantly reduced in patient stay Hercules is a clinical trial to prove efficacy of a technology and how it enhances standard care. NICE should not under estimate the importance that this treatment can offer to the future aTTP patient and the positive benefit that this can bring to a patient's well-being. TTPNetwork is aware that there is follow up built in to the Hercules trial and therefore encourage NICE to work with researchers and NHS clinicians to ensure that un-published data can be taken into consideration. This technology is the first for a very long time and the only that reduces the time spent in hospital and reduces the need for donor plasma. It has been	Thank you for your comments. Innovation will be considered as part of the appraisal process.

Section	Consultee/ Commentator	Comments [sic]	Action
		designed to treat the underlying cause of TTP. No other drug has achieved this.	
Questions for consultation	Sanofi	aTTP is not covered by the NICE blood and immune system pathway, which only refers to idiopathic thrombocytic purpura. It is expected that the health-related benefits resulting from the use of caplacizumab will be captured in the QALY calculation, with assumptions required where data is sparse. A TTP Highly Specialised Service is currently in development with NHSE. TTP is a very rare, complex condition which can present as an acute life-threatening disorder that requires prompt diagnosis, early referral and effective immediate management (as well as specialist aftercare) in a centre with comprehensive provision and a multi-discipline approach. As such, a nationally agreed approach to managing the disease in specialised regional centres is required, since currently there is significant geographic variation in mortality of aTTP patients. There may be some barriers to accessing care for aTTP for people in remote areas with limited access to specialised regional centres. Cost comparison is not appropriate in this appraisal. Caplacizumab is an add-on therapy and therefore unlikely to be similar in efficacy and resource use.	The reference to this NICE pathway has been removed.

Section	Consultee/ Commentator	Comments [sic]	Action
		The primary outcome is relevant (time to platelet normalisation, exacerbation, TTP-related mortality) although assumptions will be made to estimate long-term outcomes due to sparse data. No substantial new evidence for comparator technologies is anticipated.	
	Genetic Alliance UK	-	-
	TTP Network	There is currently sparse evidence of long term follow up care and the impact this has on preventing relapse. Long term follow care is a recent development and some hospitals still do not promote follow up care. Caplacizumab is keeping people alive by giving quicker remission. It has the potential to reduce cognitive disfunction as there would be less opportunity for thrombi in the brain etc. TTPNetwork would, as stated in previous comments, ask that NICE refer to the technology, if as we assume is appropriate, as an orphan drug as assessed by the EMA. We anticipate that this does not change things in terms of how the technology is assessed though NICE should make appropriate reference to the UK Rare Disease Strategy and the implementation plan in its remit.	Thank you for your comments.
Additional comments on the draft scope	Sanofi	-	-
	Genetic Alliance UK	Genetic Alliance UK is becoming increasingly concerned at the barrier to access to the HST programme created by the requirement that a technology is expected to be used exclusively in the context of a highly specialised service. Though clearly desirable for the delivery of complex treatments in	Thank you for your comments. NICE carefully considers the best route

Section	Consultee/ Commentator	Comments [sic]	Action
		small populations, the design and delivery of highly specialised services depends on NHS England. There has been a major decline in the design and delivery of highly specialised services since NHS England gained responsibility for them. Hardly any new Highly Specialised Services have been delivered around the advent of a new medicinal product, as has been custom prior to 2012. The slow rate of renewal of specialised commissioning in England means that there is little chance of a service being altered to take account of new treatment paradigms. Hence there is little chance of this criteria being met for conditions where no clinical intervention is currently possible. For the greatest unmet health need, Highly Specialised Technology Evaluation appears to be out of reach.	for topics during topic selection, for further details see the topic selection process for technology appraisals and highly specialised technologies.
	TTP Network	It needs to be understood that TTP is a very serious condition and many doctors do not immediately recognise it. There is strong possibility of relapse and not every episode presents the same, so is not always recognised. There is no other treatment currently other than the first line treatment of Plasma Exchange, enhanced with Rituximab, Steroids etc. This is an innovative drug focusing on the cause of TTP. The specialist centres are not yet commissioned and unlikely to be commissioned any time soon (there are delays so the proposed Autumn commissioning doesn't look like it will take place) and even when it is in place there will need to be a huge mop up of those 'lost' patients who are not being regularly followed up.	Thank you for your comments.