## Title
Accurate accounting of caplacizumab cost effectiveness



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## Accurate accounting of caplacizumab cost effectiveness

We have substantial concerns about the final input parameters in the cost-effectiveness analysis by Sanofi that was used to support the National Institute for Health and Care Excellence (NICE) recommendation for caplacizumab in acute acquired thrombotic thrombocytopenic purpura,[1] as described by Mary Hughes and colleagues.[2] With a list price of US$270 000 per course, caplacizumab warrants close scrutiny as to whether it is truly a cost-effective use of National Health Service (NHS) resources, even after incorporating the undisclosed price discounts made available by Sanofi. Unlike the current highly effective standard of care, caplacizumab does not alter the underlying pathophysiology of thrombotic thrombocytopenic purpura and is associated with an increased risk of haemorrhage and disease relapse.[3]

Our first concern is the use of risk ratios (RRs) that assume an acute mortality decrease with caplacizumab in both the decision tree (RR 0·5) and Markov models (RR 0·8).[1] The initial assumptions made by Sanofi were derived from their pooled clinical trial data, which included few deaths and were underpowered to show an overall survival benefit. NICE appropriately noted that the particularly wide confidence intervals in the data from Sanofi "included the possibility that caplacizumab increased the risk of dying"[1] from thrombotic thrombocytopenic purpura. In their final input parameters, Sanofi moderated their assumptions somewhat and used an absolute probability of death with caplacizumab (3·8%) that was no better than the 3·7% case fatality rate recently reported in a large dataset using standard of care alone.[4] Given these factors, it is unclear whether a mortality benefit of any magnitude can be attributed to caplacizumab.

Second, the Sanofi analysis applied unsupported utility values to the disease and remission states associated with caplacizumab compared with standard of care. For example, in their Markov model, the remission state following standard of care was assigned a utility value that was 34% lower than the remission state following caplacizumab treatment. This assumption aims to capture Sanofi's faith that because caplacizumab decreases the median time to platelet count normalisation by 4·6 h,[3] patients who go into remission with their drug will have fewer long-term neuropsychiatric complications than patients who go into remission with standard of care alone. However, a connection between time to platelet count normalisation and lasting neuropsychiatric outcomes has never been shown in thrombotic thrombocytopenic purpura, and the two studies cited by Sanofi did not examine these parameters.

Our third concern relates to the annual relapse rate of 1·5% used in the Markov model, which is substantially lower than described elsewhere in the literature. Caplacizumab is not disease modifying and as NICE correctly noted "would not be expected to work after people stopped having it".[1] Moreover, the Sanofi analysis does not seem to incorporate the fact that higher relapse rates were associated with the use of caplacizumab in the two clinical trials, a crucial point when considering both cost and safety. The observation that there were higher relapse rates with caplacizumab might have been driven by underpheresis in patients receiving the study drug because caplacizumab masks the thrombocytopenia of thrombotic thrombocytopenic purpura and could lead to premature discontinuation of pheresis.

The net effect of Sanofi's approach is to artificially decrease the incremental cost effectiveness ratio for caplacizumab. In an independent analysis using best-case scenario assumptions favouring caplacizumab, that ignored costs associated with bleeding complications associated with the drug and assumed preset utility values that minimised the incremental cost-effectiveness ratio, we found an incremental cost effectiveness ratio of $1·5 million per quality-adjusted life-year.[5] Accordingly, a minimum 80% price reduction would be necessary for the drug to even marginally meet the willingness-to-pay threshold in the USA, where higher willingness to pay is accepted than in the UK. Given the extensive use of unproven, optimistic assumptions around the input parameters for Sanofi's modelling, we suspect that the NHS is funding a therapy that does not meet accepted cost-effectiveness thresholds.

We declare no competing interests.

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1 National Institute for Health and Care Excellence. Technology appraisal guidance TA667: caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura. Dec 16, 2020. https://www.nice.org.uk/guidance/ta667 (accessed Dec 20, 2020).

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3 Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med* 2019; **380:** 335–46.

4 Colling M, Sun L, Upadhyay V, et al. Deaths and complications associated with the management of acute immune thrombotic thrombocytopenic purpura. *Transfusion* 2020; **60:** 841–46.

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