National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Swedish Orphan Biovitrum	Sobi consider it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No action required.
	UK ITP Forum	Yes [it is appropriate to refer this topic to NICE for appraisal]	Thank you for your comment. No action required.
Wording	Swedish Orphan Biovitrum	Sobi consider the wording of the remit of this appraisal to be appropriate.	Thank you for your comment. No action required.
	UK ITP Forum	“Avatrombopag in addition to standard of care” would be preferred to “in combination”. The latter implies that treatment should be combined with other medical treatments, but only 45% of patients in the study were on concomitant medication at baseline. The study was intended to be permissive for the addition of Ava to other medications, but this was not a requirement of the study, nor would/should it be in real world practice.	Thank you for your comment. The wording ‘in combination’ has been removed form the appraisal title.

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Timing Issues	Swedish Orphan Biovitrum	Sobi believe there is a need for NICE to appraise avatrombopag in a timely manner for the following reasons: • Avatrombopag has already been approved for use by the EMA for the ITP indication (January 2021). For patients with ITP in England and Wales, funding for avatrombopag is currently only available through individual patient referral. • Eltrombopag and romiplostim are the only licensed therapies for ITP which are NICE approved (TA221 and TA293, respectively). There is an urgent need for more licensed therapies to be made available for ITP given the chronic nature of this disorder.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	UK ITP Forum	There remains an outstanding clinical need for therapeutic alternatives to current standard of care. Some patients can be treatment refractory or intolerant of currently available agents.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
Additional comments on the draft remit	Swedish Orphan Biovitrum	None [additional comments on the draft remit].	Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK ITP Forum	N/A	Thank you. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Swedish Orphan Biovitrum	We would recommend the inclusion of more information and data on platelet counts and outcomes given it is a widely accepted endpoint for monitoring response to treatment for ITP. In addition to bleeding events, lower platelet counts in ITP have been shown to increase the risk of mortality, lower patient quality of life and increase healthcare resource utilisation (Neunert et al.,2015; Frederiksen et al.,2014; Portielje et al.,2001; Matthias et al.,2007). Although the data shows the impact of ITP is greatest when platelet counts <$30x10^9$/L, a risk of bleeding is still observed when platelet counts are between 30-$50x10^9$/L (Cines et al, 2002). In the refractory ITP setting, platelet counts of 50-$70x10^9$/L are recommended to prevent clinically significant bleeding (Rodeghiero et al, 2009). As a result, the platelet response threshold of $50x10^9$/L is an accepted measure for treatment response in both ITP clinical studies and clinical practice. Finally, across thrombocytopenia more broadly, $50x10^9$/L delineates the clinical boundary between moderate (≥$50x10^9$/L) and severe (<$50x10^9$/L) thrombocytopenia (Afdhal et al, 2008).	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.

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	UK ITP Forum	No issues identified	Thank you for your comment. No action required.
The technology/ intervention	Swedish Orphan Biovitrum	Avatrombopag received EMA marketing authorisation approval in January 2021 for the "treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)". We recommend removing the specified standard of care treatments from this statement. Although these agents were all included as standard of care treatments in the Phase III studies for avatrombopag in ITP, they are not defined in the product label.	Thank you for your comment. The wording referring to combination with standard of care has been removed.
	UK ITP Forum	Again, most patients were treated with Ava as a single agent, not in combination. Wording should reflect this. For example, could add "no additional medical treatment" to the list of examples of standard medical care.	Thank you for your comment. The wording referring to combination with standard of care has been removed.
Population	Swedish Orphan Biovitrum	Yes – the population is defined appropriately. It would be inappropriate to consider any groups within this population separately.	Thank you for your comment. No action required.
	UK ITP Forum	Definition of "chronic" keeps changing, causing confusion, especially between funders and treating physicians. "other treatments" could also be more	Thank you for your comment.

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		precise. Suggest “Adults with ITP of ≥12 months duration (chronic), refractory to one or more treatments.	
Comparators	Swedish Orphan Biovitrum	We recommend narrowing the scope of comparators to the NICE approved thrombopoietin receptor agonists (TPO-RAs), namely, eltrombopag and romiplostim only. Current guidelines for ITP following diagnosis recommend initial treatment of either corticosteroid and/or immunoglobulin therapy. Owing to the risk of adverse events and reduced long-term efficacy, corticosteroid therapy is transient, and most patients progress to receive subsequent lines of therapy (Provan et al., 2019; Neunert et al., 2019). While TPO-RAs, rituximab and splenectomy are all treatment options in the refractory setting, the TPO-RAs are considered the well-established standard of care. It would be inappropriate to include either splenectomy or rituximab given there are TPO-RA alternatives available. In the former case, clinical opinion now positions splenectomy as a later-line treatment procedure once all medical treatment options have been exhausted. For rituximab, its use is highly varied across treatment centres and lines of therapy. Therefore, it does not represent established clinical practice for the population under consideration in this appraisal. It is anticipated that the population eligible for avatrombopag will be exactly the same as those who currently receive a TPO-RA. Fostamatinib was recently approved by the EMA for chronic refractory ITP. It should not be considered a relevant comparator for this assessment given it	Thank you for your comment. At the scoping stage of the appraisal, identification of comparators should be inclusive. The potential comparators listed in the scope represent treatments used to treat moderate to chronic immune thrombocytopenia that is refractory to other treatments in NHS clinical practice. Therefore, fostamatinib has been removed from the scope. The remaining comparators are consistent with previous scopes for immune thrombocytopenia. Any exclusion from the decision problem in the company submission should be fully justified and will be considered

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		is not yet an established option for ITP, nor has it been approved by NICE, for which the respective appraisal is still ongoing. Furthermore, the manufacturer submission to NICE specifies that fostamatinib will be positioned after the TPO-RAs or where TPO-RAs are not appropriate (ID1087).	during the course of the appraisal.
	UK ITP Forum	Yes, this captures standard treatments. No single “best” alternative. Thrombopoietin receptor agonists or immunosuppression e.g. rituximab, MMF are probably the most frequently used alternatives.	Thank you for your comment. No action required.
Outcomes	Swedish Orphan Biovitrum	Yes – the outcomes are defined appropriately.	Thank you for your comment. No action required.
	UK ITP Forum	Yes [the outcome measures capture the most important health related benefits (and harms) of the technology]	Thank you for your comment. No action required.
Economic analysis	Swedish Orphan Biovitrum	[redacted]	Thank you for your comment. No action required.
	UK ITP Forum	No comments	Thank you. No action required.
Equality and Diversity	Swedish Orphan Biovitrum	It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.	Thank you for your comment. No action required.

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	UK ITP Forum	No concerns	Thank you for your comment. No action required.
Other considerations	Swedish Orphan Biovitrum	The subgroups proposed would not be appropriate for this appraisal. For rituximab, only 18.4% (n=9) patients had previously received this treatment in the trial, preventing any subgroup analysis of clinical data being performed (Study 302 CSR; data on file). For splenectomy, it is rarely considered as a treatment option for patients with ITP, clinical opinion increasingly positions this as a later-line treatment once all medical treatment options have been exhausted.	Thank you for your comment. The 'prior splenectomy' has been removed; however, the 'prior rituximab' subgroup will be considered if the evidence allows.
	UK ITP Forum	No suggestions	Thank you. No action required.
Innovation	Swedish Orphan Biovitrum	An additional, oral effective, well-tolerated treatment choice will support effective TPO-RA therapy in this patient group, controlling disease symptoms and facilitating disease control for longer. Avatrombopag is available orally without dietary restrictions and hepatoxicity monitoring which should reduce healthcare resource burden and increase likelihood of adherence compared with existing TPO-RA options (eltrombopag and romiplostim). In current clinical practice, TPO-RA treatment selection can be based on patient choice (Thachil et al., 2018).	Thank you for your comment. The appraisal committee will consider the extent to which avatrombopag is innovative in its decision making. No action required.

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		Eltrombopag is associated with food and drug restrictions which are likely to influence treatment choice and may potentially affect patient adherence. American Society of Hematology (ASH) guidelines for the treatment of ITP suggest that there may be adherence challenges with eltrombopag due to these dietary restrictions (Neunert et al., 2019). Furthermore, Eltrombopag is also associated with hepatoxicity risk which requires specific, additional patient monitoring (Eltrombopag SmPC). Romiplostim is administered via subcutaneous injection by a health care professional or may be self-administered after completing injection training (Schipperus et al.,2019). ASH guidelines for the treatment of ITP have previously suggested adherence challenges owing to this which is also a well-documented phenomenon in other chronic conditions, such as diabetes (Neunert et al.,2019; Spain et al.,2016).	
	UK ITP Forum	Yes. As an oral once daily TPO-RA, avatrombopag offers potential benefits of greater convenience that other TPO-RA e.g. a weekly subcutaneous injection (romiplostim) or an oral medication with dietary restrictions (eltrombopag).	Thank you for your comment. The appraisal committee will consider the extent to which avatrombopag is innovative in its decision making. No action required.
Questions for consultation	Swedish Orphan Biovitrum	No further comments.	Thank you. No action required.
	UK ITP Forum	Covered above. We would not consider there to be an obvious clinical subgroup that would be likely to derive particular benefit. The small patient numbers will also make sub-group analysis difficult.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Swedish Orphan Biovitrum	N/A	Thank you. No action required.
	UK ITP Forum	N/A	Thank you. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Amgen
Novartis