Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2345

avatrombopag 20mg film-coated tablets (Doptelet®)

Swedish Orphan Biovitrum Ltd

09 July 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent process

avatrombopag (Doptelet®) is accepted for restricted use within NHSScotland.

Indication under review: Treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids or immunoglobulins).

SMC restriction: to use in patients with severe symptomatic ITP or a high risk of bleeding.

In a phase III study, avatrombopag was more effective than placebo in raising and maintaining platelet counts at (or above) a minimum target level in previously-treated patients with ITP.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids or immunoglobulins).[1]

Dosing Information

The recommended starting dose of avatrombopag is 20mg taken orally, with food, once daily.

After initiating avatrombopag, the dose can be increased gradually to the maximum dose of 40mg once daily after 4 weeks based on platelet count. The lowest dose of avatrombopag to achieve and maintain a platelet count of at least 50,000/microlitre should be used. The dose adjustments are detailed in the summary of product characteristics (SPC).

Treatment with avatrombopag should be discontinued if the platelet count is greater than 250,000/microlitre after 2 weeks of dosing at 20mg once weekly, and if the platelet count does not increase to a level of at least 50,000/microlitre after 4 weeks of treatment at the maximum dose of 40mg once daily.

Avatrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Please refer to the SPC for further details.[1]

Product availability date

April 2021

Avatrombopag meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Avatrombopag is a small molecule thrombopoietin receptor agonist (TPO-RA) that increases platelet production through stimulation of proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.[1]

The key evidence supporting the efficacy and safety of avatrombopag for the indication under review comes from study 302, an international, randomised, double-blind, phase III study with a 26-week randomised treatment phase and an open-label extension phase. This study recruited adult patients who had a diagnosis of chronic ITP (≥12 months duration) according to the American Society for Hematology/British Committee for Standards in Haematology guidelines and an average of two platelet counts <30,000/microlitre (no single count should have been >35,000/microlitre). Eligible patients had received previous treatment and had initially responded to at least one prior ITP therapy or had a bone marrow examination consistent with ITP within 3 years to rule out myelodysplastic syndrome or other causes of thrombocytopenia. Patients were randomised in a 2:1 ratio to receive oral treatment with avatrombopag at a starting daily dose of

20mg (with dose titration down to 5mg or up to 40mg according to pre-specified protocol thresholds and individual response to treatment) (n=32) or placebo (n=17). Patients could be discontinued from the randomised treatment phase if the investigator considered platelet counts to be dangerously low after 7 days of treatment at the maximum dose, if patients required rescue therapy more than three times, or if they required continuous rescue therapy for more than 3 weeks. Permitted ITP concomitant background therapies, at stable doses before randomisation, included: corticosteroids, azathioprine, mycophenolate mofetil, danazol, and ciclosporin. Rescue therapy (excluding TPO-RAs) was allowed if there was an urgent need to increase platelet count. Randomisation was stratified according to splenectomy status (yes or no), baseline platelet count (≤15,000/microlitre or >15 to <30,000/microlitre), and the use of concomitant ITP medication (yes or no).[2, 3]

The primary outcome, assessed in all randomised patients, was the cumulative number of weeks of platelet response, defined as a platelet count ≥50,000/microlitre during 6 months of treatment (at visit 3 to 22 inclusive) in the absence of rescue therapy. At the end of the 6-month treatment period, avatrombopag was associated with a statistically higher cumulative number of weeks of platelet response compared with placebo. Results for the primary and secondary outcomes are shown in Table 1.[2, 3]

Table 1: Primary and secondary outcome results of study 302 in the FAS.[2, 3]

	Avatrombopag (n=32)	**Placebo (n=17)**
Cumulative number of weeks of platelet response[a]		
Mean (SD)	12.0 (8.75)	0.1 (0.49)
Median (range)	12.4 (0 to 25)	0.0 (0 to 2)
p-value	<0.001	
Platelet response rate at day 8		
Patients with response[a], %	66	0
Absolute difference (95% CI)	66 (49 to 82)	
p-value	<0.001	
Reduction in use of concomitant ITP medications from baseline.		
Patients with reduction[b], %	33 (5/15)	0 (0/7)
Absolute difference, % (95% CI)	33 (9.5 to 57)	
p-value	0.1348	

FAS=full analysis set; CI = confidence interval; SD = standard deviation. [a] platelet count ≥50,000/microlitre in the absence of rescue therapy. [b] only patients receiving concomitant ITP medication at baseline were included in the analysis.

Patients in both groups who completed 6 months of study treatment or discontinued early due to lack of treatment effects (and who had no significant safety or tolerability concerns and did not require treatment with rituximab, splenectomy, or other TPO-RA) were eligible to continue into the open-label extension phase. They were treated with avatrombopag 20mg, once daily and underwent dose titration. The overall platelet response rate observed in the core study appeared to be maintained until around week 36 of the extension phase. Beyond week 38 of the extension

phase, platelet response was lower and more variable but the low numbers of patients made interpretation difficult.[2, 3]

The submitting company conducted a Bayesian network meta-analysis (NMA) to compare TPO-RAs in adult patients with chronic ITP. The NMA included seven studies: 302[3]; 305[2], RAISE[4], Kuter et al 2008[5] (splenectomised and non-splenectomised studies); FIT1[6] and FIT2[6]. Treatments were compared on the outcomes of durable response, need for rescue therapy, reduction in the need for concomitant ITP medication, bleeding events, bleeding events with a World Health Organization (WHO) grade of 2-4, and the occurrence of any adverse event. The company concluded, that the NMA demonstrated similar efficacy between avatrombopag, eltrombopag and romiplostim.

Summary of evidence on comparative safety

Overall, the European Medicines Agency (EMA) considered that the nature and frequency of the reported adverse events were consistent with those expected after treatment of chronic ITP patients with TPO-RA. However, the safety database was considered limited. Therefore, a post-authorisation safety study has been requested to gain more data on the long-term safety profile of avatrombopag, in particular, to assess the risk of thromboembolic events, bone marrow fibrosis and myeloproliferative disease.[2]

In the randomised treatment phase of study 302, the median duration of exposure in the avatrombopag group was 26 weeks and in the placebo group was 6 weeks. Any treatment-emergent adverse event (AE) was reported by 97% (31/32) of patients in the avatrombopag group and 59% (10/17) in the placebo group and these were considered treatment-related in 62% and 18% respectively. In the avatrombopag and placebo groups respectively, patients reporting a grade 3 or higher AE were 19% versus 0%, patients with a serious AE were 28% versus 5.9%, patients with a dose increase or reduction due to treatment emergent AEs were 6.2% versus 0%, and the proportion of AEs that led to withdrawal were 9.4% versus 0%. The most frequently reported treatment-emergent AEs of any grade with an incidence >10% in the avatrombopag group versus the placebo group were: headache (38% versus 12%), contusion (31% versus 24%), upper respiratory tract infection (19% versus 5.9%), arthralgia (12% versus 0%), epistaxis (18% versus 12%), fatigue (12% versus 5.9%), gingival bleeding (12% versus 0%), and petechiae (12% versus 5.9%).[3]

Summary of clinical effectiveness issues

ITP is an acquired immune mediated disorder characterised by isolated thrombocytopenia (peripheral blood platelet count <100,000/microlitre), platelet production impairment, variable bleeding tendency and absence of any underlying cause. It is classified as acute (0 to 3 months), persistent (3 to 12 months) or chronic (≥ 12 months). Symptoms are variable, from bruising to

serious bleeding such as intracranial haemorrhage.[2] First-line treatment options for adult patients with ITP include corticosteroids, intravenous immunoglobulin (IVIg), and intravenous anti-D immunoglobulin (IV anti-D Ig). TPO-RAs eltrombopag and romiplostim have been accepted by SMC for restricted use in patients who are refractory to other treatments and with severe symptomatic ITP or a high risk of bleeding. Additional ITP treatments in the refractory setting include fostamatinib and off-label mycophenolate mofetil, rituximab, azathioprine, dapsone, and danazol.[7] Avatrombopag meets SMC orphan equivalent criteria for this indication. Clinical experts consulted by SMC considered that avatrombopag fills an unmet need in this therapeutic area, namely for additional orally administered TPO-RA.

In study 302, treatment with avatrombopag was associated with a statistically higher number of cumulative weeks with platelet count ≥50,000/microlitre over 6 months compared with placebo, which was considered clinically relevant by the EMA. This was supported by the secondary outcome of platelet response at day 8 that demonstrated a significant increase with avatrombopag compared with placebo. The secondary outcome of proportion of patients with a reduction in concomitant use of ITP medications numerically favoured avatrombopag but failed to reach statistical significance. However, the EMA considered the concomitant medications reduction effects clinically relevant, especially in patients treated with corticosteroids (due to the risk of long term-toxicity) or immunosuppressants. Pre-specified subgroup analyses were generally supportive of the primary analysis; a smaller effect size was seen in patients that were likely to have had more active disease (that is splenectomised patients, those with lower baseline platelet count and those using concomitant ITP medication).[2]

Study results, including long-term data, were limited by the very small sample size.[2] In addition, almost all patients randomised to placebo discontinued the randomised treatment phase early due to lack of efficacy and entered the open-label extension phase (88%). The median exposure duration with placebo was much shorter than with avatrombopag. This affected the assessment of the clinically relevant outcomes of bleeding events and rescue medication; no clear conclusions on the effects of avatrombopag on these could be drawn. The EMA recommended further evaluation of the long-term efficacy of avatrombopag in the post-marketing setting. The safety database was also considered limited, and a post-authorisation safety study was requested.[2]

Patients could receive some allowed concomitant ITP therapies; however, the study was not designed to assess the role of any combination therapy (for example avatrombopag in combination with corticosteroids) and the effect of any combination is uncertain.[2]

Switching from one TPO-RA to another is an option with potential for a positive effect on response and AEs.[7] In study 302, 37% of patients had previously been treated with a TPO-RA (including 20% with eltrombopag).

There is limited direct evidence versus active comparators. The submitting company performed an NMA comparing avatrombopag with active comparators and placebo. The number of studies included was limited and the sample size across studies was low. Additionally, there was

heterogeneity between the studies, however, they provide some reassurance of similar clinical effectiveness versus TPO-RA alternatives.

Clinical experts consulted by SMC considered that the place in therapy of avatrombopag is as an additional, orally administered, TPO-RA treatment (eltrombopag is also orally administered, romiplostim is for subcutaneous use).

Patient and Clinician Engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **avatrombopag, as an orphan equivalent medicine**, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Patients with refractory ITP are at increased risk of bleeding, including life threatening and fatal bleeding. The bleeding risk can be a source of anxiety for patients and their families and carers, and negatively impact their quality of life. Patients can also experience severe fatigue.
- Avatrombopag is an oral medicine that does not require fasting or other dietary modifications, which has advantages over some other ITP treatments (oral eltrombopag has dietary restrictions, romiplostim is for subcutaneous use). The lack of dietary restriction with avatrombopag would make a huge difference to the patients' daily life; it might help improve ITP treatment compliance and treatment outcomes.
- In responders, a meaningful and stable platelet count improvement is expected to result in reduced bleeding risk and symptoms. This would improve quality of life and reduce anxiety of both patients and their families and carers.
- Avatrombopag would be an additional treatment option in the armamentarium to treat ITP that does not cause immunosuppression and has a tolerable side effect profile.
- It can also be used in patients with hepatic impairment and can be titrated more easily than an alternative TPO-RA.

Additional Patient and Carer Involvement

We received a patient group submission from the ITP Support Association, which is a registered charity. The ITP Support Association has received 70% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from the ITP Support Association participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company provided a cost-minimisation analysis comparing avatrombopag to eltrombopag and romiplostim separately, for the treatment of primary chronic ITP in adult patients who are refractory to other treatments. As mentioned above, eltrombopag and romiplostim have been accepted by SMC for restricted use in patients who are refractory to other treatments and with severe symptomatic ITP or a high risk of bleeding. The time horizon used in the analysis was one year.

The clinical data used to underpin the assumptions of comparable efficacy and safety between treatments were taken from a NMA as described above. The NMA found that avatrombopag was likely to be similar to comparators in terms of durable response, need for rescue therapy, reduction in use of concomitant ITP medications, any bleeding events or any adverse events.

Medicine acquisition, administration and monitoring costs were included in the analysis. No costs were included for adverse events, non-compliance or subsequent treatment of 'drop-outs' for any treatment, which was consistent with the assumption of comparable efficacy and safety profiles across treatments. The dosages of avatrombopag (20mg once daily) and eltrombopag (50mg once daily) used in the analysis were consistent with the starting dosage stated in each medicines SPC. The dosage of romiplostim used (3µg/kg once weekly) was selected on the basis of advice from an expert panel of UK clinicians.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is also in place for eltrombopag.

The base case results using list prices for all medicines are presented in Table 2. The results presented do not take account of the PAS for eltrombopag or the PAS for avatrombopag but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for eltrombopag due to commercial confidentiality and competition law issues.

Table 2: Base-case results using list prices for all medicines

Treatment	Total cost (per patient per year)	Incremental cost/saving (per patient per year)
Avatrombopag	£25,487	-
Eltrombopag	£22,147	£3,340
Romiplostim	£29,593	-£4,106

A negative figure denotes cost savings for avatrombopag

A number of scenario analyses were included in the company's submission which are shown in Table 3. These scenario analyses explore the impact on results of accounting for, among other assumptions, differences in the dosage of new patients initiating treatment versus stable patients who have been receiving treatment for 6 months, as well as an assumption of no vial wastage for romiplostim. These scenarios indicate that conclusions using the company's base case results were robust to changes in the majority of parameters included in the model.

Table 3: Scenario analyses using list prices for all medicines

Total cost (per patient per year)	Intervention	Comparator		Incremental cost/saving (per patient per year)	
	Avatrombopag	Eltrombopag	Romiplostim	Eltrombopag	Romiplostim
Base case	£25,487	£22,147	£29,593	£3,340	-£4,106
Minimum dose	£5,465	£7,132	£17,061	-£1,668	-£11,597
Maximum dose	£48,847	£32,157	£92,253	£16,690	-£43,406
New patients	£26,481	£23,315	£40,679	£3,166	-£14,198
Stable patients	£25,120	£22,668	£42,125	£2,452	-£17,005
No administration costs	£25,487	£22,147	£27,191	£3,340	-£1,704
Wastage costs	£25,487	£22,147	£29,484	£3,340	-£3,997

A negative figure denotes cost savings for avatrombopag

The key limitation with the analysis was that there is no direct evidence comparing avatrombopag against the comparators included in the analysis and therefore the company had to present NMAs to underpin the assumptions of comparable efficacy and safety across treatments that are required to validate the use of a cost-minimisation analysis. There was a high degree of uncertainty surrounding the results of the NMAs as indicated by the width of the credible intervals.

The Committee considered the benefits of avatrombopag in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as avatrombopag is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted avatrombopag for restricted use in NHSScotland.

Additional information: guidelines and protocols

An international consensus report on the investigation and management of primary immune thrombocytopenia was published in 2010 and was subsequently updated in 2019.[7] The initial recommended treatment for ITP is steroids, and IV anti-D Ig can also be used, followed by medical therapies and then surgical interventions (splenectomy, only after failure of medical therapies and depending on patient age and comorbidities). Subsequent medical therapies with robust evidence

include TPO-RAs (eltrombopag, avatrombopag and romiplostim), rituximab and fostamatinib. The guidance make specific recommendations for patients who have failed multiple prior therapies, and recommends that consideration is given to the use of other medical therapies if not already used. The list of treatments included in the guideline is mycophenolate mofetil, fostamatinib, rituximab, azathioprine, dapsone, and danazol. Switching from one TPO-RA to another is also an option and have been shown to have a positive effect on response and AEs.[7]

A multidisciplinary guideline panel from the American Society of Haematology reported on the investigation and management of primary immune thrombocytopenia in 2019.[8] Similar to the International consensus report, it recommends, in patients who are corticosteroid-dependent or do not have a response to corticosteroids, TPO-RA (either eltrombopag or romiplostim) rather than rituximab and rituximab over splenectomy. However, It acknowledged that there is no single optimal second-line treatment and that treatment should be individualized based factors such as the duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of the patient, medication adherence, patient values and preferences, cost, and availability.[8]

Additional information: comparators

Eltrombopag, romiplostim.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Avatrombopag	**Initial dose of 20mg once daily, with dose adjustment to maintain a platelet count >50,000/microlitre using the lowest dose necessary; minimum dose 20mg once weekly; maximum dose of 40mg once daily.**	**First year: 4,096 to 45,184.** **Subsequent year: 3,328 to 46,592.**

Costs from BNF online on 5 March 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 100 patients eligible for treatment with avatrombopag in year 1 rising to 102 year 5. The uptake rate was estimated to be 27% in year 1 (27 patients) and 72% in year 5 (73 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

These estimates do not take account of any patient access schemes applied to displaced medicines.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 15 April 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive

access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.