Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Integrated Care Partnership - Surrey Downs, Guildford & Waverley, North West Surrey, and East Surrey Places & associated partner organisations.

NICE Technology Appraisals (TA) for local implementation

NICE TA Guidance name and number	Avatrombopag for treating primary chronic immune thrombocytopenia TA853		
Available at	https://www.nice.org.uk/guidance/ta853		
Date of issue	15 Dec 2022	**Implementation deadline**	15 March 2023

Medicine details[1]	
Name and brand name	Avatrombopag (Doptelet®)
Manufacturer	Swedish Orphan Biovitrum
Mode of action	Avatrombopag is an orally active, small molecule thrombopoietin (TPO) receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production.
Licensed indication	Doptelet® is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
Formulation	Each film-coated tablet contains avatrombopag maleate equivalent to 20 mg of avatrombopag.
Dosage	Treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases. Doptelet® should be taken at the same time of day (e.g. in the morning or evening) with food, including when taking the dose less frequently than once daily. Initial dose regimen: The recommended starting dose of Doptelet® is 20 mg (1 tablet) once daily with food. Monitoring and dose adjustment: After initiating therapy, assess platelet counts at least once weekly until a stable platelet count ≥ 50 x 109/L and ≤ 150 x 109/L has been achieved. Dose adjustments (see Table 2 and Table 3 of SmPC - *https://www.medicines.org.uk/emc/product/11837*) are based on the platelet count response. Do not exceed a daily dose of 40 mg (2 tablets). Discontinuation:

	Discontinue avatrombopag if the platelet count does not increase to ≥ 50 x 109/L after 4 weeks of dosing at the maximum dose of 40 mg once daily. Discontinue Doptelet® if the platelet count is greater than 250 x 109/L after 2 weeks of dosing at 20 mg once weekly.
Comparison of NICE TA with Summary of Product Characteristics (SmPC)[2]	The dosage and time intervals are the same as NICE evaluation. *This is the current dose considered by NICE as part of this NICE evaluation. Subsequent changes in the license following NICE publication will need to be considered by the Area Prescribing Committee and will not be routinely funded by local commissioners, as the incremental cost per QALY would not have been considered.*

NICE TA recommendations[2]

Recommendations

Avatrombopag is recommended, within its marketing authorisation, as an option for treating primary chronic immune thrombocytopenia (ITP) refractory to other treatments (for example, corticosteroids, immunoglobulins) in adults. It is only recommended if the company provides it according to the commercial arrangement.

Decision making framework (DMF)

National guidance and priorities

The ICS has a legal obligation to commission this medicine in line with the NICE TA.

- This NICE TA has been assigned an implementation deadline of 3 months.
- The implementation deadline is 15 March 2023.

Clinical effectiveness

Current treatment for newly diagnosed primary chronic ITP usually includes corticosteroids and immunoglobulins. This is followed by thrombopoietin receptor agonists (TPO-RAs). Avatrombopag is another TPO-RA.

Clinical trial evidence shows that avatrombopag is more effective than placebo at increasing the number of platelets in the blood (cells that help the blood to clot) to a level that meaningfully reduces the risk of bleeding. Avatrombopag may be as effective as other TPO-RAs, but it has only been compared with them indirectly, which is uncertain.

There are also uncertainties with some assumptions in the economic modelling. Despite this, avatrombopag is likely to provide benefit for people who have primary chronic ITP. Also, the cost-effectiveness estimates are below what NICE normally considers an acceptable use of NHS resources. So, avatrombopag is recommended.

Patient safety

- The product should be used within its product license.
- This is a Black Triangle drug – all suspected adverse reactions should be reported.

Patient factors

- An additional treatment option would be valued by patients.

a. Treatments for ITP which need to be injected can cause increased anxiety, soreness and bruising. Patients plan their life around injection dates, and ensure the safe storage and administration of these treatments.
b. The other oral TPO-RA can cause side effects including chronic gastrointestinal issues and increased risk of blood clots. It can also be affected by diet, and people taking it may need to restrict what foods they eat, and when they eat them. This may have a large effect on everyday life, adherence to treatment and effectiveness.
c. Some treatments for ITP also cause immunosuppression, which increases the risk of infection. Infections can cause a drop in platelet count, which may need hospitalisation and rescue therapy if uncontrolled.

- Avatrombopag is an oral treatment with no dietary restrictions and no immunosuppression and would be an advance in ITP treatment in the UK.

- This medicine is available under a homecare service so will be delivered directly to the patient.

Environmental impact

No statement on environmental impact was made in the NICE TA.

- This is an oral medicines which has some packaging waste but less than for sub-cutaneous injections.

Equality & diversity

No statement on equality and diversity was made in the NICE TA.

- Age – avatrombopag has a marketing authorisation for treatment in adult patients only.

Note: Drugs approved by NICE for adult conditions will be commissioned in children at specialised paediatric centres if the patient meets the NICE criteria and there is evidence to suggest that the drug is safe and clinically appropriate to use in children as per the NHS England Medicines for Children Policy (see https://www.england.nhs.uk/publication/commissioning-medicines-for-children-specialised-services/ and a Blueteq form is available.

Place in therapy relative to available treatments

The ITP pathway on the Surrey PAD is based on the pathway from St George's Hospital, our tertiary provider and local consultants have deemed this to be outdated and a review is required.

In addition to avatrombopag, another treatment for ITP, fostamatinib has recently had a NICE TA published (Overview | Fostamatinib for treating refractory chronic immune thrombocytopenia | Guidance | NICE), which also needs to be included in the pathway.

NICE states:

In regard to positioning of avatrombopag:
'When someone is diagnosed with ITP, they have an 'initial' treatment that includes corticosteroids, immunoglobulins or both. The clinical experts explained that TPO-RAs would not be used before corticosteroids and immunoglobulins but would be used if this initial treatment failed. The committee concluded that avatrombopag is likely to be used after initial treatment of newly diagnosed chronic ITP.'

In regard to the relevant comparators for avatrombopag:
'In its submission, the company considered other TPO-RAs (eltrombopag and romiplostim) to be the only appropriate comparators for avatrombopag. The company's rationale for this was that:
• TPO-RAs are considered to be well-established standard care for ITP
• it would be inappropriate to consider rituximab or surgical splenectomy as the comparators given the availability of 2 other TPO-RAs.

The ERG agreed that the company's positioning of avatrombopag was reasonable. But it highlighted uncertainty around the variations in rituximab use in clinical practice. The committee queried at what point in the treatment pathway TPO-RAs are prescribed in the NHS. The clinical experts explained that, while *care is individualised to people with ITP, clinicians generally use TPO-RAs before rituximab.* They also explained that, before the COVID-19 pandemic, rituximab's use varied across the UK. *But international guidance changes have caused a shift in practice to use TPO-RAs first after initial treatment has failed.* This is because rituximab can suppress the immune system. They also confirmed that clinicians rarely offer splenectomy in the first year of diagnosis and do not consider it as an alternative to TPO-RAs.

Stakeholder views

The paper was sent out for consultation and *x* comments were received.

Cost-effectiveness

Section 1: cost of the technology

a. Annual cost per patient (or complete course if shorter) for both primary and secondary care:

The list price of a 10-tablet pack of avatrombopag 20 mg is £640.00 (excluding VAT; BNF online, accessed June 2022).

Dose	Cost
20mg daily	£23,360
40mg daily	£46,720

b. Availability of CAP/PAS price:
The company has a commercial arrangement. This makes avatrombopag available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

c. Price relative to comparable medicines:

The relevant comparators are the other TPO-RAs - eltrombopag and romiplostim.

Further details of the TPO-RA are as follows:

TPO-RA details	Licensed indication	NHS indicative price November 2022 BNF	Approximate annual cost*
Romiplostim Nplate® sc injection. Dose: maximum once weekly dose of 10mcg/kg should not be exceeded.	…adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)	125 microgram = £241 250 microgram = £482	£241 x 52 w = £12,532 £482 x 52 w = £25,064 The maximum dose for an adult weighing 75kg would be 750mcg a week and the annual cost would be £75,192
Eltrombopag Revolade® Film coated tablets. Dose: no more than 75mg daily	…patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)	28 x 25mg = £770 28 x 50mg = £1,540 28 x 75mg = £2,310	£770 x 12m = £9,240 £1,540 x 12m = £18,480 £2,310 x 12m = £27,720

*This does not include application of the discount patient access scheme by manufacturers.

Section 2: NICE resource impact statement and template

a. NICE resource impact statement
No significant resource impact is anticipated.

We do not expect this guidance to have a significant impact on resources; that is, the

resource impact of implementing the recommendations in England will be less than £5 million per year (or approximately £9,000 per 100,000 population, based on a population for England of 56.3 million people).

This is because avatrombopag is a further treatment option for patients alongside other thrombopoietin receptor agonists and the overall cost of treatment for this patient group will be similar.

b. NICE resource impact template
Not supplied.

Drug costs for Surrey Heartlands:
Currently, the pathway allows for the sequential use of eltrombopag and romiplostim. There is no current guidance which makes recommendations on sequential use to include avatrombopag or and distinction between the TPO-RAs to give a preferred product or sequence.

The drug costs would be significant if sequential use of all three TPO-RAs is accepted.

Commentary:
Although NICE states that a significant impact on resources is not expected, there is still a new cost pressure even though this may be below the £9,000 per 100,000 population threshold for NICE, as this TA represents a new line of treatment.

At £9,000 per 100,000 population, this represents:

	East Surrey	Guildford and Waverley	Surrey Downs	North West Surrey	Surrey Heartlands ICB
Population*	193,532	232,784	316,690	388,466	1,131,472
Cost	£17,418	£20,951	£28,502	£34,962	£101,832

* August 2022 population figures from NHS Prescription Services through ePACT.

The Surrey Heartlands Director of Pharmacy and Medicines Optimisation has delegated authority to enable the Committee to be a decision-making committee providing the impact of any single decision does not exceed £100,000 within an individual Place per annum. Decisions with a cost impact of over £100,000 within an individual Place per annum require authorisation from Surrey Heartlands Health & Care Professionals Committee at their next meeting. Exception to this will be for any decision made in relation to a NICE Technology Appraisal (which are subject to requiring mandatory funding by commissioners) and other urgent items. The exceptions will be taken to the next Executive Meeting (which meets weekly) for authorisation.

Traffic light recommendation to APC

NHS Payment Scheme (NHSPS) excluded high-cost drug:
Yes.

Recommended traffic light status and rationale:
RED – Specialist ONLY drugs - treatment initiated and continued by specialist clinicians.

PAD definitions, available at: Traffic Light Status (res-systems.net)

Implementation

NICE TA implementation must be within 3 months of publication.
Actions to implement:

a. Primary care
- This is a National Tariff excluded high-cost drug and is commissioned by ICSs for use in secondary care. There should be no prescribing in primary care.
- Primary care prescribers should be aware that their patient is receiving this medicine and ensure that this is recorded in the patient's notes in order to be alert to potential side-

effects and interactions with other medicines prescribed in primary care. This will also ensure that GP records, which are accessed by other healthcare providers, are a true and accurate reflection of the patient's medication.
- Avatrombopag is an oral medicine which has no dietary restrictions and no immunosuppression, which is an advantage over other treatments for ITP.

b. Secondary care
- Providers are NHS hospital trusts.
- Trusts to follow internal governance procedures to add to their formulary and initiate homecare.
- The initiation, administration and on-going treatment is managed by secondary care.
- Specialists will be required to notify the high-cost drugs teams of initiation and response to treatment using the Blueteq® system.
- Homecare arrangements will be managed by the trust.

c. ICS
- This technology is commissioned by integrated care systems.
- The current ICS pathway is based on that from St George's and is deemed to be outdated as
    - practice has changed over the COVID-19 pandemic (before the COVID-19 pandemic rituximab use was variable but now TPO-RAs are used first after initial treatment has failed) and
    - the introduction of this medicine and another new medicine in a new class, fostamatinib, which has a NICE TA for use after TPO-RAs or if TPO-RAs are unsuitable.
- The pathway needs to be revised in conjunction with St George's Hospital, our tertiary provider.

d. PAD and Joint Formulary
- Addition to the Surrey PAD as per process
- Remove the current ITP pathway from the PAD

Proposed tick box forms

Blueteq® forms have been developed and included below.

Additional information required for Joint Formulary:
None currently identified.

References:

1 Specification of Product Characteristics. emc. Available at: Doptelet 20 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Accessed <3.1.23>

2 NICE Technology Appraisal Guidance: Avatrombopag for treating primary chronic immune thrombocytopenia. Technology appraisal guidance [TA853]Published: 15 December 2022 . Available at: Overview | Avatrombopag for treating primary chronic immune thrombocytopenia | Guidance | NICE Accessed <3.1.23>

3 NICE Resource Impact Report: Avatrombopag for treating primary chronic immune thrombocytopenia. Technology appraisal guidance [TA853]Published: 15 December 2022 . Available at: Resource impact statement | Avatrombopag for treating primary chronic immune thrombocytopenia | Guidance | NICE Accessed <3.1.23>