Urgent Interim Commissioning Policy Proposition

Peginterferon alfa-2a and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (all ages) [2420]

Summary

NHS England has confirmed that peginterferon alfa-2a and ropeginterferon alfa-2b will be made available as treatment options for people with myeloproliferative neoplasms (MPNs) within the criteria set out in this urgent interim commissioning policy position during the period of supply disruption of peginterferon alfa-2a which is expected to be until July 2025.

Links and updates to other policies and documents

This policy relates to the following guidance, practices, and specification:

Ruxolitinib for treating polycythaemia vera Technology appraisal guidance (TA921) Published: 18 October 2023.

National Comprehensive Cancer Network (NCCN) Guideline for Essential Thrombocythaemia 2024. Published 8 August 2024 NCCN Guideline for Essential Thrombocythemia 2024

British Society of Haematology (BSH) Guideline: Diagnosis and management of polycythaemia vera. Published: 27 November 2018.

British Society for Haematology Guideline A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis. Published November 2018.

British Society for Haematology Guideline: Diagnosis and evaluation of prognosis of myelofibrosis. Published November 2023.

British Society for Haematology Guideline: The Management of Myelofibrosis. Published November 2023.

Plain language summary

About myeloproliferative neoplasms

Myeloproliferative neoplasms (MPNs) are blood cancers in which the bone marrow makes too many cells that are either released into the blood stream or build up inside bone marrow. This includes polycythaemia vera (PV) where too many red blood cells are made, essential thrombocythaemia (ET) where too many platelets are made, and myelofibrosis, where the bone marrow is less stable and patient prognosis is typically five years or less. Complications of these conditions can include thromboembolic events (such as blood clots, strokes and heart attacks), increased risk of bleeding or

infection (due to altered levels of blood cells) and in some cases, progression to more severe blood cancers such as myelofibrosis and acute myeloid leukaemia.

About peginterferon alfa-2a

Peginterferon alfa-2a is indicated in the treatment of chronic hepatitis B (HBV) and chronic hepatitis C (HCV). However, its use in in these conditions has reduced significantly due to other treatments being available. There is still some usage of peginterferon alfa-2a in certain scenarios, including HBV- hepatitis D (HDV) super-infection. Peginterferon alfa-2a is also widely used off-label to treat MPNs such as PV, ET and (less frequently) myelofibrosis. It is given via subcutaneous injection (under the skin).

About ropeginterferon alfa-2b

Ropeginterferon alfa-2b is indicated as monotherapy in adults for the treatment of PV without symptomatic splenomegaly. The use of ropeginterferon alfa-2b in other MPNs is off-label. It is given via subcutaneous injection (under the skin). Expert working group (EWG) consensus is that peginterferon alfa-2a and ropeginterferon alfa-2b have clinical equivalence in the treatment of essential thrombocythaemia and myelofibrosis, and there is published evidence of its equivalence in the treatment of polycythaemia vera.

Epidemiology and needs assessment

It is estimated that there are more than 2000 people in the UK receiving peginterferon alfa-2a for MPNs. Due to increased demand, including the expanded use of peginterferon alfa-2a following its inclusion in oncology guidelines and patients typically using peginterferon alfa-2a for an increasingly extended period, global demand has increased significantly. As a result, there is a supply issue with peginterferon alfa-2a, expected to last until at least July 2025, so alternative treatment options may need to be considered. The main alternative option is ropeginterferon alfa-2b.

Commissioning position

The commissioning position is that peginterferon alfa-2a and ropeginteferon alfa-2b are recommended to be available as a treatment option for people with myeloproliferative neoplasms, within the criteria set out in this document. The policy proposition is restricted to treatment of children over three years old[1] with peginterferon alfa-2a and the treatment of adults[2] with ropeginterferon alfa-2b in line with the market authorisation.

Inclusion criteria

Essential thrombocythaemia

[1] Peginterferon alfa-2a can be used in children three years and older via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children).

[2] Ropeginterferon alfa-2b can be accessed for use in post-pubescent children via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children).

Patients are eligible for treatment with peginterferon alfa-2a or ropeginterferon alfa-2b if they fulfil the following criteria:

- Defined as in the high-risk category[3].

OR

- Have extreme thrombocytosis >1500x10^9/L.

OR

- Low risk with debilitating symptoms.

AND

- Hydroxycarbamide treatment is contraindicated or inappropriate or has failed.

AND

- Treatment with alternative agents listed below is contraindicated or inappropriate or has failed:
    - Anagrelide.
    - Busulfan (in those with limited life expectancy eg less than ten years).

Polycythaemia vera

Patients are eligible for treatment with peginterferon alfa-2a or ropeginterferon alfa-2b if they fulfil **ONE** of the following:

- Defined as in the high-risk category[4].

OR

- Those who have had a disease-related major haemorrhage.

OR

- Patients aged less than 65 years otherwise considered low risk[5] with at least one of the following:
    - Cardiovascular risk factors.
    - Elevated white blood cell (WBC) count >15 x 10^9/L.
    - Extreme thrombocytosis >1000 x 10^9/L.
    - JAK2 variant allele frequency >50%.
    - Haematocrit uncontrolled with venesection eg > 4 venesections per year.

AND either:

[3] Thrombosis history, disease related major haemorrhage or age >60 years - NCCN Guidelines: https://pubmed.ncbi.nlm.nih.gov/38269572/.
[4] Age ≥65 years and/or prior PV-associated arterial or venous thrombosis - BSH guideline 'Diagnosis and management of polycythaemia vera (2018)'.
[5] BSH guideline 'Diagnosis and management of polycythaemia vera (2018)'.

- Hydroxycarbamide treatment and ruxolitinib treatment[6] (in line with NICE TA 921) is contraindicated or inappropriate or has failed.

  OR

- Patient is eligible and enrolled in the Mithridate trial[7] (see Appendix 1).

Myelofibrosis

Patients are eligible for treatment with peginterferon alfa-2a or ropeginterferon alfa-2b if they are:

- Defined[8] as low risk or intermediate 1 with debilitating symptoms, leukocytosis >15 x10^9/L, or extreme thrombocytosis >1000 x 10^9/L.

AND

- Treatment with alternative agents is contraindicated or inappropriate or has failed.

Maximisation of supply

During the period of supply shortages, access to peginterferon alfa-2a (and possibly ropeginterferon alfa-2b) may be difficult to predict. Should shortages reach a point where greater control of stocks is required, more targeted use of peginterferon alfa-2a is likely to be required amongst patients who fulfil the eligibility criteria:

- Patients already established on peginterferon alfa-2a should be reviewed at the earliest opportunity to ensure they fit the inclusion criteria as set out in this policy and are eligible for continuation of treatment with peginterferon alfa-2a or alternatively, switching to ropeginterferon alfa-2b. If not, patients should be switched to the appropriate alternative therapy.
- **All** patients on peginterferon alfa-2a or ropeginterferon alfa-2b should have their dosing optimised as laid out in the Dosing section.
- If there is insufficient peginterferon alfa-2a and ropeginterferon alfa-2b to treat all patients who meet the eligibility criteria outlined in this policy, then patients may need be treated in order of clinical priority. This should be discussed by a local multidisciplinary team, taking into account the individual patient, the local population alongside peginterferon alfa-2a allocation. Suggested Tiers are:
  - Tier 1: High risk polycythaemia vera patients, high risk essential thrombocythaemia patients, pregnant patients or those trying to

[6] Overview | Ruxolitinib for treating polycythaemia vera | Guidance | NICE Ruxolitinib is recommended, within its marketing authorisation, for treating polycythaemia vera in adults who cannot tolerate hydroxycarbamide (also called hydroxyurea) or when the condition is resistant to it.
[7] Patients eligible for the Mithridate trial can be enrolled and started on appropriate treatment without trying all alternative treatments listed below. Patients on the Mithridate trial receiving peginterferon alfa-2a should be prioritised to continue the treatment – see appendix for further information.
[8] British Journal of Haematology | Wiley Online Library.

conceive[9], those in the Mithridate clinical trial, myelofibrosis patients with past history of thrombosis/bleed.

- Tier 2: People of childbearing age where alternative treatments are not available, low risk polycythaemia vera/essential thrombocythaemia patients, patients with low risk/ intermediate-1 myelofibrosis.

Exclusion criteria

Patients where there is a contraindication to either peginterferon alfa-2a or ropeginterferon alfa-2b, as outlined in the summary of product characteristics (SmPC).

Stopping criteria

Treatment with peginterferon alfa-2a or ropeginterferon alfa-2b should be discontinued in those who experience side-effects, including but not limited to: new or worsening eye disorders that cannot be attributed to alternative causes, organ toxicities, neuropsychological issues or endocrine toxicities.

Clinicians considering a drug holiday for their patient should discuss each case with their regional MDT with relevant MPN specialist input.

Monitoring requirements

Monitoring requirements and initiation of/transitions between treatments are patient specific and are to be determined by the consultant in charge of the patient's care. Full blood counts, biochemistry profiles, liver function tests and thyroid function tests should be monitored every 2–4 weeks during the initial three months of interferon therapy. Patients with CrCl < 30 may require a lower-than-expected dose or require more frequent monitoring and should be treated with increased caution.

Dosage

Peginterferon alfa-2a or ropeginterferon alfa-2b is commissioned within the criteria in the urgent interim commissioning policy. The following approaches should be used during the period of shortage of peginterferon alfa-2a to ensure that patients with the highest clinical risk and the maximum number of patients can be treated with the stock that is available. Peginterferon alfa-2a or ropeginterferon alfa-2b with the lowest acquisition cost should be used. Ropeginterferon alpha-2b is available as a pre-filled syringe (PFS) – PFS allows for adjustable dosing increments ideally in multiples of 50 micrograms, however for those requiring fine adjustments the pen wheel operates each click and each dot in the dosing window represents 5 micrograms (i.e. 10 clicks per 50 micrograms denomination).

Starting new patients on peginterferon alfa-2a:

- Starting dose 90 micrograms fortnightly.

[9] This may include males who are at high risk as they may require interferon for conception, females who are high risk and planning or are pregnant and those patients requiring treatment for pregnancy related issues (2 or more early pregnancy losses, or one late pregnancy event, or IVF). As detailed in British Society for Haematology Guideline A guideline for the management of specific situations in polycythaemia vera and secondary erythrocytosis. Published November 2018.

- Up titrate in increments of whole syringes as tolerated until optimal response achieved noting that slow dose escalation is often better tolerated.
- When a stable target response is reached (e.g. for 3 months) consider spacing doses further apart.
- Maximum dose is 180 micrograms weekly.

Starting new patients on ropeginterferon alfa-2b:

- Starting dose 125 micrograms fortnightly.
- Up titrate if required after 6-8 weeks until optimal response achieved noting that slow dose escalation is often better tolerated.
- When a stable target response is reached (e.g. for 3 months) consider spacing dosing to monthly to minimise the number of pens used. For example, 125 micrograms dosed 4 weeks apart and then 4 weeks before commencing the next pen. This equates to using 6 pens per 12 months, with 125 micrograms given every 4 weeks.
- Dose permitting, the pre-filled pen should be used up to two times within 30 days in line with the SmPC.
- Maximum dose is 500 micrograms every two weeks.

The following approaches should be considered **to optimise use in those that remain on peginterferon alfa-2a treatment**:

- Dosing should be optimised to whole syringes.
- Consider spacing doses further apart with a minimum of fortnightly doses.

Transitioning patients from peginterferon alfa-2a to ropeginterferon alfa-2b

Patients with high-risk disease that is responsive to peginterferon alfa-2a should remain on interferon treatment (whichever preparation is available) but should avoid switching between treatments multiple times.

In the event of significant depletion in peginterferon alfa-2a stock and NHS England commissioning of ropeginterferon alfa-2b, patients meeting the above-outlined criteria should be transitioned based on the following dosing strategies:

Patients receiving weekly doses of peginterferon alfa-2a

Peginterferon alfa-2a Weekly Dose	**Suggested ropeginterferon alfa-2b fortnightly dose***
45 micrograms	**Consider optimising peginterferon to 90 micrograms every 2 weeks** **Or** **65-125 micrograms ropeginterferon alfa-2b****
90 micrograms	**125 micrograms**
135 micrograms	**200 micrograms**

180 micrograms	**250 micrograms**

Patients receiving 2-weekly/fortnightly doses of peginterferon alfa-2a

Peginterferon alfa-2a 2 Weekly Dose	**Suggested ropeginterferon alfa-2b monthly dose***
45 micrograms	**Consider optimising peginterferon alfa-2a to 90 micrograms every 4 weeks*****
90 micrograms	**125 micrograms**
135 micrograms	**200 micrograms**
180 micrograms	**250 micrograms**

*Not an exact conversion but doses can be changed according to haematological response i.e. dose of ropeginterferon alfa-2b = 70% dose of peginterferon alfa- 2a.

** depending on the tolerated dose by the patient. if the starting dose of peginterferon alfa-2a was 45mcg weekly aim to titrate to ropeginterferon alfa-2b 125mcg monthly when able.

***Where possible patients requiring lower doses than 125micrograms of ropeginterferon alfa-2b every 30 days should be prioritised for peginterferon alfa-2a to ensure cost effectiveness and minimal wastage.

Proposed Governance arrangements

A clinician considering prescribing a medication outside the terms of the licence (‘off-label’) should do so in accordance with MHRA and GMC guidance which apply throughout England. The GMC guidance states prescribing unlicensed medicines may be necessary where ‘there is no suitably licensed medicine that will meet the patient’s need’. Should clinicians consider this appropriate for their patients and they have followed local medicines governance arrangements for off-label use, then NHS England will reimburse the off-label use of ropeginterferon alfa-2b or peginterferon alfa-2a within the criteria set out in this urgent interim commissioning policy.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Audit requirements

Provider organisations must register all patients using prior approval software and ensure audit arrangements are in place to demonstrate compliance against the criteria as outlined in this policy proposition.

Policy review date

If a review is needed due to a new evidence base, then NHS England should be contacted at this email address: england.CET@nhs.net. This statement will be reviewed in July 2025. This may be sooner if circumstances change or there is a recognised need, including when ropeginterferon alfa-2b as a treatment for polycythaemia vera without symptomatic splenomegaly is appraised by NICE.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the three nation's values. Throughout the development of the policies and processes cited in this document, we have:

> Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
>
> Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Acute Myeloid Leukaemia (AML)	AML is a cancer of the white blood cells that progresses quickly and aggressively, and usually requires immediate treatment.
Bone Marrow	Bone marrow is the soft, spongy tissue in the centre of bones. It contains stem cells that produce blood cells and the cells that make up the immune system.
Myelofibrosis	An uncommon type of bone marrow cancer that causes extensive scarring in the bone marrow, disrupting the normal production of blood cells. Myelofibrosis often causes an enlarged spleen.
Splenomegaly	An enlarged spleen can have many causes including blood cancers
Thrombocytosis	A disorder in which your body produces too many platelets. Reactive thrombocytosis or secondary

	thrombocytosis is when the cause is an underlying condition, such as an infection. When the high platelet count is due to the presence of mutations such as JAK2, CALR or MPL, the disorder is called essential thrombocythaemia and is a blood and bone marrow disease.

Appendix 1: Mithridate trial

Patients eligible for the Mithridate trial can be enrolled and started on appropriate treatment without trying all alternative treatments listed in the Inclusion Criteria stated in this policy document.

Consider for the Mithridate trial[9] patients with polycythaemia vera if they are eligible for the trial and meet **all** of the following:

- Been diagnosed in last 15 years and treated with one cytoreductive drug or not for 10 years or less (without resistance or intolerance).
- WBC >11 (at any time since diagnosis).
- A high risk feature such as age >60 years, thrombosis, haemorrhage, treated diabetes or hypertension or platelets >1000.

Patients on the Mithridate trial receiving interferon therapy should be prioritised to continue the treatment.

The Mithridate study contact email is: mithridate@trials.bham.ac.uk