NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Spesolimab for treating generalised pustular psoriasis flares

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using spesolimab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: [January 2025]

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using spesolimab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 14 February 2025
- Second evaluation committee meeting: TBC
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Spesolimab is not recommended, within its marketing authorisation, for treating generalised pustular psoriasis (GPP) flares in adults.

1.2 This recommendation is not intended to affect treatment with spesolimab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

There is no licensed standard care for GPP flares, so the clinical evidence is from a comparison of spesolimab with placebo for the treatment of moderate-to-severe GPP flares. It shows that spesolimab resolves flares faster than placebo, but it is uncertain how it affects the rate of hospital and intensive care admissions, or the length of hospital stays.

There are uncertainties in the economic evidence for spesolimab because:

- the clinical evidence used to model treatment response is uncertain, and
- the treatment of subsequent flares was not included.

Because of these uncertainties, it is not possible to determine the most likely cost-effectiveness estimates for spesolimab. So, it is not recommended.

2 Information about spesolimab

Marketing authorisation indication

2.1 Spesolimab (Spevigo, Boehringer Ingelheim) is indicated ‘for the treatment of flares in adult patients with generalised pustular psoriasis’.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for spesolimab.

Price

2.3 The list price for spesolimab is £15,000 for 2 450-mg vials (excluding VAT; BNF, accessed December 2024).

2.4 The company has a commercial arrangement (simple discount patient access scheme), which if it had been recommended, would have made. spesolimab available to the NHS with a discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Boehringer Ingelheim, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Generalised pustular psoriasis (GPP), also known as von Zumbusch psoriasis, is a rare form of psoriasis. It is characterised by flares, during which pustules appear all over the body, but especially in skin folds, the genital regions and the fingertips. Large areas of the skin also become inflamed. Other symptoms of GPP flares include fever, swelling, joint pain and fatigue. GPP flares can be life threatening if left untreated, because they can lead to organ failure. The disease course may be unpredictable. People living with GPP experience a substantial negative impact on their daily activities, social interactions and mental wellbeing, which extends to their loved ones. The patient expert explained that it can be difficult to get a diagnosis and that the fear and anxiety of a flare can be all consuming. Patient experts reported that GPP flares make it difficult to wear clothing

because it is painful when anything touches the skin during a flare. The physical appearance of the condition can be very stressful and cause anxiety. The committee recognised the substantial impact GPP flares have on physical and mental health. It acknowledged the unmet need for effective treatments for GPP flares. The committee concluded that people with GPP would value a treatment option with faster flare resolution and control, with tolerable side effects.

Clinical management

Treatment pathway and positioning

3.2 There are no licensed treatments and no specific guidelines in the UK for GPP flares, so best available care (BAC) draws on treatments licensed for other forms of psoriasis (see section 3.3). BAC treatments can be slow to elicit response, often do not fully resolve symptoms and have notable side effects. The company proposed that spesolimab would be expected to replace current first-line and subsequent treatments for GPP flares. The EAG was unable to obtain further clinical expert opinion for verifying the appropriate positioning of spesolimab in the treatment pathway. Clinical experts at the committee meeting confirmed that spesolimab would be offered alongside first-line treatment of GPP flares. The committee concluded that spesolimab could be used in first-line treatment of GPP flares.

Comparators

3.3 The company did a structured expert elicitation (SEE) exercise to collect information on BAC, in terms of the efficacy and safety profiles of the treatments used in the NHS for GPP flares. The exercise comprised 2 rounds of elicitation (individual and group round), concluding in an expert consensus response to questions. The company used data from the SEE exercise to inform the model for BAC treatments from the end of week 1 through to the end of the time horizon. These active treatments included:

- topical steroids, ciclosporin, methotrexate, acitretin or infliximab at first-line treatment (week 1)
- biologicals including infliximab, guselkumab, ustekinumab or secukinumab at second-line treatment (weeks 2 to 4)
- biologicals including guselkumab, ustekinumab or secukinumab at third-line treatment (week 5 and later).

Clinical experts stated that the treatments that reasonably reflect the BAC for GPP flares in the NHS are:

- ciclosporin or acitretin (used in some parts of the UK) at first line (week 1)
- infliximab and methotrexate at second-line treatment (weeks 2 to 4)
- other biologicals at third-line treatment (week 5 and later).

The current BAC also includes rest, hydration, pain medicine and topical emollients. The committee concluded that current BAC for GPP flares in the NHS is mainly ciclosporin at first line (week 1), and in some parts of the UK acitretin is also used at first line. At second line (weeks 2 to 4) infliximab with methotrexate is used and third-line treatments (week 5 and later) are biologicals (guselkumab, ustekinumab or secukinumab). The committee concluded that the relevant BAC comparators for spesolimab as a first-line treatment for GPP flares are ciclosporin and acitretin.

Clinical effectiveness

Effisayil 1 trial

3.4 The key clinical evidence came from the Effisayil 1 trial (n=53) a multicentre, randomised, double-blind phase 2 study comparing spesolimab with placebo for treating moderate-to-severe GPP flares in adults. Before randomisation, participants had to stop biological therapies, systemic non-biological therapies and other treatments such as

phototherapy and topical treatments. Participants were randomised on day 1 to have 900 mg intravenous spesolimab or placebo. Escape treatment during days 2 to 7 was allowed for worsening disease, with these people deemed non-responders in day 8 analyses. Placebo response data from the Effisayil 1 trial was unavailable because over 80% of people who had placebo switched to spesolimab on day 8. From day 9 to week 12, safety was assessed, and people who had recurrent flares could have a 900-mg rescue dose of spesolimab. Beyond week 12, people with no flare symptoms could enter the Effisayil ON extension study.

Trial results

3.5 The primary outcome of the Effisayil 1 trial was Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 at week 1. The secondary outcome was GPPGA total score of 0 or 1 at week 1. The clinical experts agreed that using a GPPGA pustulation subscore of 0 or 1 appropriately reflects the resolution of a flare, with 0 being completely resolved. But, the GPPGA pustulation score is not used in the NHS and the extent of visible pustules is assessed instead. The proportion of people who achieved a GPPGA pustulation subscore of 0 or 1 (clear or almost clear skin) was higher in the spesolimab arm compared with the placebo arm, with a risk difference of 46.0%. The committee concluded that spesolimab was more effective than placebo in resolving GPP flares, but there is uncertainty in the size of the treatment effect. This is because in the trial people in the placebo arm did not have systemic biological or systemic non-biological treatments and only had supportive care such as hydration, pain medicines and emollients.

Generalisability of Effisayil 1

3.6 Because the Effisayil 1 trial enrolled adults with GPP presenting with moderate-to-severe flares, it was uncertain whether the trial was generalisable to people with mild flares. Clinical experts explained that the

majority of flares they treat range from moderate-to-severe, and mild flares are likely to progress to moderate or severe flares relatively quickly. The clinical experts anticipated that all people with GPP flares would be offered spesolimab, regardless of flare intensity, and using spesolimab for mild flares could reduce exacerbation of the flare. The EAG had concerns about the generalisability of the Effisayil 1 trial results to the UK. A high proportion (55%) of the people in the Effisayil 1 trial were Asian because 51% of the trial sites were in Asia, compared with only 30% from Europe. None of the trial sites were in the UK. People in the trial were slightly older than people with GPP flares in the NHS, with more women enrolled than men. Clinical experts stated that gender is not a treatment effect modifier. Clinical expert opinion was that the trial was representative of the ethnicity of people with GPP flares in the NHS. But they added that about half the people treated for GPP flares in the NHS would be on maintenance biological therapies for concomitant plaque psoriasis. The committee concluded that all people with GPP flares of all intensities are expected to be offered spesolimab in clinical practice. It also concluded that the ethnicity of the people in the trial is generalisable to the NHS. It noted that there were trial participants from Japan. Clinical expert opinion was that more data on spesolimab use in Japan could aid decision making. The committee also concluded that evidence in the first week of the trial is not generalisable to the NHS. This is because it provides no evidence on the efficacy of spesolimab in people who are having other biological treatments as maintenance therapy for concomitant plaque psoriasis.

Cost effectiveness

Company's economic model

3.7 The company used a Markov model with 3 health states:

- GPP flare, which is the state everyone starts in and is defined, as per Effisayil 1 trial, as:
  - GPPGA total score of 3 or more

  - new or worsening pustules
  - GPPGA pustulation subscore of 2 or more, and
  - 5% or more of body surface area with erythema and the presence of pustules
- resolved flare (GPPGA pustulation subscore 0 or 1) and
- death.

The cycle length was 1 day, and the time horizon was 12 weeks. For the economic model, response to treatment was modelled in terms of flare resolution, defined as a GPPGA pustulation subscore 0 or 1. The committee concluded that the model was suitable for decision making but noted uncertainty about several model assumptions and inputs (see sections 3.8 to 3.13). These uncertainties included how BAC efficacy (see section 3.10) and composition (see section 3.9) was modelled, lack of subsequent flare modelling, and the impact on hospitalisation rates.

The modelling of BAC treatments

3.8 For week 1 in the company's model, the source of BAC treatment composition and costs was the placebo arm of Effisayil 1, in which people had no standard care treatments. This approach ensured consistency with the trial design but raised concerns about alignment with clinical practice. After week 1 the company used the SEE exercise to inform the modelling of comparator treatments and costs. This was because of cross over to open-label spesolimab from day 8 for people in the placebo arm. The EAG preferred to use the SEE exercise to model BAC treatments and costs in week 1 and after instead, because it could better capture treatments used in the NHS. Clinical experts stated that it is unlikely that people with a GPP flare would not be offered any pharmacological treatment for a week. The committee acknowledged that the SEE exercise is a lower-quality source of evidence than a clinical trial. But it concluded that it was still an appropriate source to inform the costs and treatments of

the BAC arm for week 1 and after week 1. This is because the estimates could be more aligned with NHS clinical practice.

The modelling of BAC efficacy

3.9 In week 1 of the company model, treatment response to BAC was taken from the Effisayil 1 trial. The EAG and committee noted that people in the placebo arm of the Effisayil 1 trial did not have any pharmacological standard care treatments for flares. This did not align with clinical practice. For response after week 1, the company used data from the Effisayil 1 historical cohort to model the efficacy of BAC. This cohort, from the same population as the trial, provided information on resolution of past GPP flares. But the Effisayil 1 historical cohort lacked GPPGA pustulation subscore data and the company used time-to-pustular-clearance as a proxy for the GPPGA pustulation subscore outcome. The EAG noted the limitations of using the historical cohort as the lack of standardised definitions for flare severity, absence of data on flare duration, and lack of GPPGA pustulation subscore data. The EAG also raised issues about the lower-than-expected biologicals use in the historical cohort compared with the NHS. It therefore preferred the SEE exercise but noted it is a lower-quality evidence source than real-world evidence. The committee preferred the historical cohort to inform BAC efficacy in the model because it involves the same population as the Effisayil 1 trial. This ensures consistency by maintaining the same data source for week 1 and the subsequent weeks. The committee concluded that separate scenarios using the SEE exercise and the historical cohort to inform BAC treatment response for week 1 and after would be helpful. These would allow the uncertainty caused by the limitations of the SEE exercise and the trial to be explored (see section 3.4).

12-week time horizon

3.10 The model assumes that all GPP flares in both arms will have responded by week 12. The time is consistent with the follow-up period of Effisayil 1.

But, the assumption of flare resolution by week 12 overlooks evidence from Effisayil 1. It showed that only 25 of the 35 people assessed at week 12 had a GPPGA pustulation subscore of 0 (n=21) or 1 (n=4), while 10 people had escape therapy. The response status of their flares was unknown. Also in the Effisayil 1 historical cohort, 12% of GPP flares had not responded by week 12. The EAG highlighted that it was difficult to model a longer time horizon reliably because of the limited 12-week evidence. Clinical experts noted that it is clinically reasonable to assume that all GPP flares have responded to treatment (both to spesolimab and to BAC) by week 12 in the model. The committee concluded that a 12-week time horizon sufficiently reflects time for treatment response.

Implementing a second flare

3.11 The company did not incorporate second flares into the model. It justified this assumption citing clinical expert validation that GPP flares respond within 12 weeks. The trial reported that 11.3% of people had rescue treatment with spesolimab for second flares, and 8 people had BAC escape therapy after day 8. The company stated that evidence suggests people are unlikely to experience more than 2 flares per year. The EAG noted that this does not stop the possibility of 2 flares happening in a 12-week period. It also raised concerns that treating a flare with spesolimab could potentially affect the efficacy or safety of subsequent treatments for the flare, which is not captured in the current model. Clinical experts noted that the likelihood of a second GPP flare depends on the resolution of the initial flare. People who have GPPGA pustulation subscores of 0 or 1 (resolved) within 12 weeks are unlikely to have another flare and their flares are considered fully resolved. But, people with only partially controlled flares are at higher risk of another flare within 12 weeks. The clinical experts highlighted that GPP is an episodic disease characterised by periods of flares and remission, with unresolved cases potentially leading to 2 or 3 flares per year, though this varies significantly between people. The committee concluded that not implementing a

second flare in the model did not align with the fact that people could have a subsequent flare within 12 weeks. The committee also concluded that not implementing a second flare in the model introduces uncertainty about the long-term effectiveness and safety of spesolimab. Scenario analysis implementing a second flare would aid decision making.

Mortality

3.12 The company assumed that there is an increased mortality risk associated with a GPP flare for people in intensive care. The company applied a daily rate of death of 0.096% for people in intensive care. This was derived from a French National Health System database study, in which 2.6% (15 of 569) people died within 4 weeks after their last flare. The company used all-cause and disease-related mortality for resolved GPP flares in both the intervention and comparator arms. Following clinical expert opinion, the committee concluded that it did not accept the assumption that people treated with spesolimab have a 0% probability of being admitted to intensive care (see section 3.13).

Inpatient and intensive care rates

3.13 The company model assumes faster flare resolution with spesolimab, with reduced hospitalisation rates and reduced intensive care admission rates. The company assumed that 77.6% of people having BAC were hospitalised for treatment of GPP flares (Wolf et al. 2024). The company assumed that only 38.8% of people having spesolimab would be hospitalised. This was calculated by applying a 48.4% relative reduction in active flare rates (defined as a GPPGA pustulation subscore greater than 1) from Effisayil 1 to the proportion hospitalised having BAC. The company model assumes that GPP flares treated with spesolimab never require intensive care admission, whereas some people having BAC do need intensive care admission. The exact proportion is confidential and cannot be reported here. The EAG questioned whether the reduction in hospitalisation rates assumed for spesolimab is too optimistic, given that

there is no empirical evidence available from the trial. It also raised the issue of double counting the treatment benefits of faster flare resolution, reduced probability and duration of hospitalisation, reduced intensive care admissions, and reduced mortality. Clinical experts stated that it is realistic to expect that using spesolimab will lead to fewer hospital admissions and faster flare resolutions, leading to shorter hospital stays. They also stated that it is unlikely that GPP flares treated with spesolimab would not require intensive care admission. This is because people with GPP may have comorbidities that mean intensive care admission is needed to treat the flare. The committee agreed that if UK data for inpatient and intensive care admission rates are not available, then it would prefer data from Wolf et al. It noted that using the 77.6% value from Wolf et al., with a reduction of about 50% to bring the assumed inpatient rate to 38.8%, is a generous upper bound estimate. Clinical experts stated that in the NHS, GPP flares are treated with BAC rather than placebo, so the difference in efficacy between spesolimab and placebo may be overestimated in the trial. For estimating the proportion requiring intensive care admission, it preferred to use the 11.5% proportion for the BAC arm and reduce this proportionally for the spesolimab arm. The committee concluded that it would prefer more UK clinical data on inpatient and intensive care admission rates and duration of stay for GPP flares treated with BAC and spesolimab, if available.

Severity

3.14 The company did not make a case for the severity modifier to be applied.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.15 The committee took into account the patient access scheme for spesolimab and commercial arrangements (such as simple discounts or biosimilar prices) for the comparator treatments. Cost effectiveness was

assessed by calculating incremental cost-effectiveness ratios (ICERs) for spesolimab compared with current BAC without spesolimab. The committee concluded that it could not identify an ICER that reflected its preferred assumptions.

Committee's preferred assumptions

3.16 The committee's preferred assumptions included:

- current BAC being ciclosporin and acitretin at first line (week 1)
  - SEE exercise used as the most appropriate source to inform the composition and costs of treatments in the BAC arm for week 1 and after week 1 (see section 3.8)
- Effisayil 1 historical cohort used to inform treatment response in the BAC arm for week 1 and after week 1 (see section 3.9)
- a second flare implemented within 12 weeks in the model to align with clinical practice based on recurrence from Effisayil 1 trial (see section 3.11)
- Wolf et al. (2024) used to estimate spesolimab inpatient rate at 38.8% (see section 3.13)
- use of spesolimab does not lead to no (0%) intensive care admissions (see section 3.13)
- if no suitable data is found on the reduction in intensive care from spesolimab use, then a 50% relative reduction can be used as an upper bound (see section 3.13).

The requested additional analyses to aid decision making includes:

- clinical data on the inpatient and intensive care admission rates for BAC and spesolimab, ideally from UK registry data or UK real-world evidence (see section 3.13)
- scenario analyses of SEE exercise to inform BAC efficacy (see section 3.9)

- any additional insights that can be provided from data on spesolimab use in Japan (see section 3.6)
- scenario analysis of a second flare implemented within 12 weeks in the model (see section 3.11)
- data on the use or market share of the comparator treatments to verify the BAC cost estimates from the SEE exercise (see section 3.7)
- data on the treatment distribution for BAC (see section 3.3)
- scenario analyses on the reduction in mortality benefit of spesolimab (see section 3.4).

Acceptable ICER

3.1 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically around:

- whether spesolimab reduces mortality, hospital and intensive care admission rates
- the source of data used to inform the composition and costs of comparator arm for the economic model
- the source of data used to inform the efficacy of the comparators in the economic model.

So, the committee was unable to identify an acceptable ICER that aligned with its preferences.

Other factors

Equality

3.2 Clinical expert opinion assured the committee that there was no concern about the GPPGA pustulation subscore underestimating severity in people with darker skin. This is because assessment is based on the visibility of pustules and not the observation of redness, which is less visible on dark skin. Clinical experts confirmed that ethnicity is not a prognostic characteristic. The committee concluded that there are no other equality issues.

Managed access

3.3 The company did not make a proposal for managed access after carrying out a feasibility assessment. It concluded that current UK data sources do not allow use of routinely collected data to reduce uncertainties and there are no appropriate processes in place to establish new data collection. Clinical expert opinion was that data collection is possible.

Uncaptured benefits

3.4 The committee considered whether there were any uncaptured benefits of spesolimab. It identified reduction in mortality as an additional benefit of spesolimab not captured in the economic modelling. So, the committee concluded that scenarios showing the reduction in mortality benefit would aid decision making.

Conclusion

Recommendation

3.5 The committee acknowledged the high uncertainty associated with the clinical evidence and economic modelling for spesolimab. It decided that more evidence was needed to generate robust cost-effectiveness estimates. It noted that the EAG's and company's base cases were also uncertain, and that the most plausible cost-effectiveness estimates were above the range normally considered a cost-effective use of NHS

resources. So, it did not recommend spesolimab for treating GPP flares for routine use in the NHS.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Baljit Singh

Vice chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Madiha Adam

Technical lead

Rufaro Kausi

Technical adviser

Jeremy Powell and Louise Jones

Project managers

Emily Crowe

Associate director

ISBN: [to be added at publication]