NICE National Institute for Health and Care Excellence

NICE guidance

Spesolimab for treating generalised pustular psoriasis flares

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Spesolimab is recommended as an option for treating generalised pustular psoriasis (GPP) flares in adults, only if it is used to treat:

- initial moderate to severe flares when:
  - the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score is 3 or more (at least moderate), and
  - there are fresh pustules (new appearance or worsening of existing pustules), and
  - the GPPGA pustulation subscore is at least 2 (at least mild), and
  - at least 5% of the body's surface area is covered with erythema (abnormal redness of the skin or mucous membranes) and has pustules
- subsequent flares with a GPPGA pustulation subscore of 2 or more (at least mild), if the last flare was treated with spesolimab and resolved to a GPPGA pustulation subscore of 0 or 1 (clear or almost clear skin).

  Spesolimab can only be used if the company provides it according to the commercial arrangement.

1.2 A second dose of spesolimab can be used after 8 days if a flare has not resolved to a GPPGA pustulation subscore of 0 or 1.

1.3 Take into account how skin colour could affect the GPPGA score and make any adjustments needed.

1.4 These recommendations are 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. Usual treatment includes ciclosporin, acitretin and biological treatments used to treat other forms of psoriasis.

The licence for spesolimab does not include definitions for initial or subsequent GPP flare severity. For this evaluation, the severity definition used for initial flares is based on the criteria used in the clinical trial. The severity definition used for treating subsequent flares and retreating initial and subsequent flares are based on the criteria used in the economic model. Clinical advice is that these definitions align with how spesolimab would be used in clinical practice.

Clinical trial evidence shows that spesolimab resolves moderate to severe GPP flares faster than placebo. But it is uncertain how it affects the proportion of people who need hospital and intensive care admissions, or the length of hospital stays. There is no evidence comparing spesolimab with usual treatments used for GPP flares in the NHS.

The cost-effectiveness estimates for spesolimab are uncertain. This is because of uncertainties with the clinical evidence and assumptions used in the economic model around inpatient and intensive care admissions and spesolimab's long-term effects. But there are also potential benefits not captured in the model. These include the potential for people to have fewer biological treatments for future GPP flares and the potential to live longer if they have spesolimab compared with usual treatment.

When taking this into consideration, the most likely cost-effectiveness estimates for spesolimab are within the range that NICE considers an acceptable use of NHS resources. So, it is 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. This makes spesolimab available to the NHS with a discount. The size of the discount is commercial in confidence.

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 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 clinical experts at the second committee meeting highlighted that GPP is an episodic disease characterised by periods of flares and remission. Unresolved cases can potentially lead to 2 or 3 flares per year, though this varies significantly between people. The patient expert also explained that, for some people, symptoms may not fully resolve between flares. 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 clinical experts explained that some existing treatments for GPP can have serious side effects (see section 3.2). The committee concluded that people with GPP would value a treatment option with faster flare resolution and control, and 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 work, often do not fully resolve symptoms and have 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 get further clinical expert opinion to verify the appropriate positioning of spesolimab in the treatment pathway. Clinical experts at the first committee meeting confirmed that spesolimab would be offered as a first-line treatment of GPP flares. At the second meeting, the committee noted that spesolimab is the first targeted treatment for GPP flares, so would also be used to treat subsequent flares. It concluded that spesolimab could be used in first-line and subsequent treatment of GPP flares.

Comparators

3.3 The company did a structured expert elicitation (SEE) exercise to collect efficacy and safety profiles of the BAC treatments used in the NHS for GPP flares. The exercise comprised 2 rounds of elicitation (an individual and a group round), concluding in an expert consensus response to questions. The company's SEE exercise identified that active treatments for BAC included:

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

The current BAC also includes rest, hydration, pain medicine and topical emollients. The committee agreed 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 at third-line (week 5 and later), biological treatments such as guselkumab, ustekinumab or secukinumab are used. The committee concluded that the relevant BAC comparators for spesolimab as a treatment for GPP flares are ciclosporin, acitretin and biological treatments.

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. It compared spesolimab with placebo for treating moderate to severe GPP flares in adults. It defined moderate to severe GPP flares as:

- a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 3 or more (at least moderate), and
- presence of fresh pustules (new appearance or worsening of existing pustules), and
- a GPPGA pustulation subscore of at least 2 (at least mild), and
- at least 5% of the body's surface area covered with erythema (abnormal redness of the skin or mucous membranes) and the presence of pustules.

Before randomisation, participants had to stop biological treatments,

systemic non-biological treatments and other treatments such as phototherapy and topical treatments. Clinical experts highlighted that this was not reflective of NHS practice, where many people would be having concomitant biological treatments for plaque psoriasis. 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 single 900-mg dose of spesolimab. Beyond week 12, people with no flare symptoms could enter the Effisayil ON extension study. The committee was concerned that:

- the follow-up period in the Effisayil 1 study was only 12 weeks
- there was only 1 week of comparative data available because of the high crossover rate from the placebo to the spesolimab arm and
- people had to stop concomitant biological treatments before entering the study.

It concluded that these issues introduced considerable uncertainty into the Effisayil 1 trial results.

Trial results

3.5 The primary outcome of the Effisayil 1 trial was 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 (clear or almost clear skin) appropriately reflects the resolution of a flare, with 0 being completely resolved. They explained that the GPPGA pustulation subscore is not currently 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 was higher in the spesolimab arm compared with the placebo arm, with a risk difference of 46.0%. The committee concluded that the Effisayil 1 trial suggested that spesolimab was more effective than placebo in resolving GPP

flares. But there was uncertainty in the size of the treatment effect caused by limitations of the trial design and generalisability of the population (see section 3.4 and section 3.6).

Generalisability of Effisayil 1

3.6 At the first meeting, the EAG raised concerns about the generalisability of the Effisayil 1 trial results to the UK population. This was because:

- 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. Also, people in the trial were slightly older than people with GPP flares in the NHS and more women were enrolled than men.
- The Effisayil 1 trial enrolled adults with GPP presenting with moderate to severe flares (that is, a GPPGA total score of 3 or more), so it was uncertain whether the trial was generalisable to people with mild flares.
- People in Effisayil 1 had to stop biological treatments before entering the trial, with a washout period to ensure no effects of previous treatments remained.

  Clinical expert opinion at the first meeting was that the trial was representative of the ethnicity of people with GPP flares in the NHS. Also, that gender is not a treatment effect modifier. The committee agreed that the ethnicity of the people in the trial is generalisable to the NHS. It considered whether spesolimab would be used in clinical practice in people who had mild flares. At the first meeting, the clinical experts explained that most GPP flares range from moderate to severe, and mild flares are likely to progress to moderate or severe flares quickly. They 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. But, at the second meeting, the committee was concerned that there was no clinical effectiveness evidence for treatment of mild GPP flares with spesolimab. The clinical expert at the second meeting agreed that it was reasonable to align the population having spesolimab with that in the Effisayil 1 trial. They noted that the GPPGA total score and the GPPGA pustulation subscore were not

currently used in clinical practice to define a flare. But, healthcare professionals would start to use these scores to identify moderate to severe flares and define resolution of these flares if included in any recommendation for spesolimab (see section 3.5). The committee agreed that the initial flare treated with spesolimab should be moderate to severe, as defined by the criteria in Effisayil 1 based on the GPPGA total and pustulation subscores, to align with the clinical evidence (see section 3.4). The clinical experts also highlighted that about half the people who have treatment for GPP flares in the NHS would be on maintenance biological treatments for concomitant plaque psoriasis. At the second meeting, the clinical expert explained that spesolimab would be started for a GPP flare, even if people were already having biological treatments for concomitant plaque psoriasis. The committee was concerned that because there would be no washout period for biological treatments in the NHS, they would have a short-term benefit even if stopped when starting spesolimab. The committee agreed that concomitant biological treatments might be a treatment effect modifier, so the Effisayil 1 trial may overestimate the relative effect for spesolimab compared with clinical practice. It noted that there was no clinical evidence for spesolimab in people who had concomitant biological treatments. It also noted that spesolimab may reduce the need for maintenance treatment when introduced into the treatment pathway because it is the only effective treatment for controlling GPP flares (see section 3.22). The committee concluded that because the trial only contained data for moderate to severe flares, it would take account of this in its decision making. Also, the lack of concomitant biological treatments means that evidence in the first week of the Effisayil 1 trial is not generalisable to the treatments used for GPP in the NHS.

Cost effectiveness

Company's economic model

3.7 In its original submission, the company used a Markov model with 3 health states:

- GPP flare (as defined in Effisayil 1; see section 3.4), which is the state everyone starts in

- resolved flare (GPPGA pustulation subscore 0 or 1) and
- death.

After consultation, the company introduced additional health states to capture people having a subsequent flare (see section 3.11). 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 company's model after consultation, in general, was suitable for decision making but noted uncertainty about several model assumptions and inputs. These uncertainties included the modelling of subsequent flares (see section 3.13), the mortality impact for spesolimab (see section 3.14), potential treatment waning (see section 3.15) and impact on hospitalisation rates (see sections 3.16 and 3.17).

The modelling of BAC treatments

3.8 At the first committee meeting, the company used the following sources to inform the composition and costs for BAC in the model:

- For week 1 the company used the placebo arm (week 1) of Effisayil 1, in which people had no standard care treatments.
- 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.

At the first committee meeting, the EAG preferred to use the SEE exercise to model BAC treatments and costs from the first day in the model, because it captured treatments used in the NHS better. 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 is more aligned with NHS clinical practice. So, at the first meeting the committee preferred to use the SEE exercise to inform the costs and treatments of the BAC arm from the first day in the model. The company and

EAG updated their base case at the second committee meeting to include the committee's preferred assumption.

The modelling of BAC efficacy

3.9 At the first committee meeting, the data for spesolimab came from the full follow-up period of the Effisayil 1 trial. The company used different sources for week 1 and after week 1 to inform the response for BAC. For week 1, it used the data from week 1 of 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 (see section 3.6). For response after week 1, the company used data from the Effisayil 1 historical cohort to model the efficacy of BAC. This study collected data from people before they entered the Effisayil 1 trial and provided information on resolution of past GPP flares. But the Effisayil 1 historical cohort lacked GPPGA pustulation subscore data so the company used time-to-pustular-clearance as a proxy for the GPPGA pustulation subscore outcome. At the first committee meeting, the EAG noted the limitations of using the historical cohort because of the lack of standardised definitions for flare severity and the lack of flare duration and GPPGA pustulation subscore data. The EAG also raised issues about the lower-than-expected use of biological treatments in the historical cohort compared with the NHS. So the EAG preferred the SEE exercise but noted it is a lower-quality evidence source than real-world evidence. At the first meeting, the committee noted the uncertainty in the estimates but still preferred to use the historical cohort to inform BAC treatment response in the model. This was because it included the same population as the Effisayil 1 trial. The company and EAG updated their base case after consultation to align with this preference. They also provided scenarios using the SEE exercise to inform the treatment response from the start of the modelled time horizon. In these scenarios, they varied the proportions of people from the SEE exercise with severe and moderate severity flares and the GPPGA pustulation subscore used to define flare resolution. The committee agreed that scenarios using the SEE exercise were useful but maintained its preference from the first meeting. It concluded that the Effisayil 1 historical cohort should be used to inform BAC treatment effect from the start of the modelled time horizon to align with the population in the model and trial.

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 25 of the 35 people who had spesolimab assessed at week 12 had a GPPGA pustulation subscore of 0 (n=21) or 1 (n=4) and 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. The committee recalled that NICE's manual on health technology evaluations states that a short time horizon can be justified if there is no differential mortality effect between technologies and the differences in costs and clinical outcomes relate to a relatively short period. Clinical experts at the first meeting 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. But, at the second meeting, the committee noted that people may have multiple flares in their lifetime (see section 3.1) and the 12-week time horizon assumed equal costs and quality of life associated with each flare. The committee queried if this was plausible or if the treatment effect would change for first and subsequent flares. It noted that the 12-week time horizon made the modelling of treatment waning and long-term mortality challenging (see section 3.14 and section 3.15). At the second meeting, a patient organisation representative highlighted the results of an internal survey. In this, over half of people with GPP had experienced more than 10 flares and all 21 respondents had had more than 1 flare. So, theoretically spesolimab could be used many times by the same person. The committee agreed that a 12-week time horizon may sufficiently reflect time for treatment response to an initial flare. But, whether this is replicable for subsequent flares outside of this period is unknown. It concluded that the 12-week time horizon introduced considerable uncertainty to the cost-effectiveness model, but the lack of long-term data for spesolimab made modelling a longer time horizon extremely challenging.

Subsequent flares

Subsequent flares in people with GPP

3.11 At the first committee meeting, the company assumed people in the model only had 1 flare in the 12-week period. It justified this assumption citing clinical expert validation that GPP flares respond within 12 weeks. The committee recalled that some people could have multiple flares per year (see section 3.10). The company stated that evidence suggests people are unlikely to experience more than 2 flares per year. At the first meeting, clinical experts noted that the likelihood of a second GPP flare soon after the initial flare can depend 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 in this time period and their flares are considered to be fully resolved. But people with only partially controlled flares are at higher risk of another flare within 12 weeks. At the second meeting, the committee recalled its concerns about the ability of the 12-week time horizon to capture the full impact of subsequent flares. It concluded that a second flare should be included in the model, but that this did not capture the impact of subsequent flares over the lifetime of a person with GPP.

Defining a subsequent flare

3.12 At consultation, the company updated its base case to include a subsequent flare for a proportion of people in the model. The committee noted that a subsequent flare was defined differently in the Effisayil 1 trial and company's model. The company's model definition was broader than that in the trial. It included people with a GPPGA pustulation subscore of 2 or more who had not had escape therapy with BAC during the first 7 days after the first dose. The committee noted that a GPPGA pustulation subscore of 2 was defined as mild pustulation, whereas initial flares were modelled as being moderate to severe (a GPPGA total subscore of 3 or more). The clinical expert explained that the modelled definition aligned with how spesolimab would be used in clinical practice to treat subsequent flares, including those that did not occur shortly after the initial flare. This was because spesolimab is likely to be used earlier to treat subsequent flares than for an initial flare. This aims to reduce symptoms and to minimise the need for hospitalisation for the subsequent flare. The committee noted that the company had modelled a

subsequent flare to only occur in people whose initial flare had responded to treatment (defined in the model as a GPPGA pustulation subscore of 0 or 1). It considered that subsequent flares in these people may be likely to respond to spesolimab, so healthcare professionals may want to start spesolimab when symptoms first present. Clinical experts also highlighted that the presentation of GPP is highly variable and that there are some people who have episodic flares on a background of ongoing symptoms despite biological treatment. The committee recalled that these people were most likely to have a subsequent flare within 12 weeks of their initial flare (see section 3.11). But, clinical experts explained that it was unlikely that subsequent flares would respond to spesolimab if the initial flare had not resolved with treatment. So, spesolimab would not be used in these cases. The committee concluded that it was acceptable for the company to define subsequent flares as those with a GPPGA pustulation subscore of 2 or more and assume that they would only be treated if the initial flare had resolved to a GPPGA pustulation subscore of 0 or 1 with spesolimab.

Modelling a subsequent flare

3.13 The Effisayil 1 trial reported that 11.3% of people had treatment with spesolimab for a subsequent flare (that is, an additional dose during weeks 2 to 12). The company's base case after consultation assumed that:

- 7.14% of people in the spesolimab and BAC arms had treatment for a subsequent flare. This was based on the number of people who had treatment for a subsequent flare in Effisayil 1 whose:
  - initial flare resolved to a GPPGA pustulation subscore of 0 or 1
  - subsequent flare met the definition used in the company's model (see section 3.12).
- There were equal rates of subsequent flares in the spesolimab and BAC arms.
- The same proportion of people in the spesolimab arm had an extra dose at day 8 for non-response for first and second GPP flares. This contrasted with the Effisayil 1 trial, where no day-8 dose was allowed for people having spesolimab for subsequent flares.

The clinical expert agreed that the modelled proportion of people having a subsequent flare was reasonable. The committee noted that spesolimab aims to treat and not prevent flares, so the company's assumption of equal rates of subsequent flares in the BAC and spesolimab arm was plausible. But this was highly uncertain and not informed by data. This is because a high number of people crossed over to spesolimab in the BAC arm at day 8 in the Effisayil 1 trial. The committee also considered whether the same proportion of people would have an extra dose at day 8 for their initial and subsequent flare. The clinical expert stated that an additional dose of spesolimab would be considered for a subsequent flare that had not resolved to a GPPGA pustulation subscore of 0 or 1 at day 8. The committee recalled that subsequent flares were modelled to occur when there had been a response to spesolimab for their initial flare (see section 3.12). So, it was likely that fewer people in this population would need additional doses of spesolimab at day 8 than seen in the trial. Also, some people whose flares meet the criteria for non-response at day 8 might choose alternative biological treatments instead of retreatment with spesolimab. This is because they are likely to have severe flares, may be very unwell and their flares have only partially responded to the previous dose. The committee noted that the company had provided scenarios assuming different treatments for subsequent flares that have not resolved to a GPPGA pustulation subscore of 0 or 1 at day 8. It agreed that this was an appropriate measure of response to use for subsequent flares and considered these scenarios in its decision making. The committee agreed that the company's modelling of a subsequent flare, including the relative rate of occurrence and treatments used at day 8 for non-response, was highly uncertain. But it used the company's analyses including a subsequent flare in its decision making.

Mortality

3.14 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. At the first committee meeting, the committee agreed that it was plausible that people whose flares were severe enough that they are admitted to intensive care, would have an increased risk of death. It noted that the difference in total quality-adjusted life years (QALYs) between spesolimab and BAC was small because of the short time horizon modelled. But it recalled that spesolimab was the first effective treatment for treating GPP (see section 3.5). So, the committee considered it to be plausible that a long-term benefit for spesolimab from reducing mortality during subsequent flares had not been captured in the modelled 12-week time horizon (see section 3.10). At consultation, the company provided scenarios including a lifetime mortality benefit for spesolimab (the exact figure is confidential and cannot be reported here). It calculated this by assuming that spesolimab prevents 1% of deaths and people with GPP have:

- 1 flare per year
- an average life expectancy of 16 years after entering the model, based on the average age of people in the POLARIS trial and an elevated mortality risk for people with GPP compared with the general public from Ericson et al. (2023).

The EAG could not replicate the company's scenario and was not clear how the lifetime mortality benefit had been implemented. It was concerned that the company's calculation did not include discounting or account for differences in mortality by age or because of comorbidities. It was also concerned that the calculation was based on a cohort with different baseline characteristics to Effisayil 1. Clinical experts at the second meeting thought that spesolimab may be associated with a long-term mortality benefit. This was because current BAC treatments sub-optimally manage flares so are associated with poor outcomes. With long-term use they can also cause serious adverse events, such as recurrent systemic inflammation and renal failure, which can increase mortality. The committee acknowledged it was plausible that spesolimab was associated with a long-term mortality benefit that was not fully captured in the EAG or company base case. But the size of this benefit was uncertain. It thought that the high uncertainty around spesolimab's treatment effect (see section 3.6) and concerns with the company's implementation of a long-term mortality benefit made it inappropriate to include this in the model. The committee concluded that the long-term effect on mortality of using spesolimab to treat subsequent GPP

flares was highly uncertain and remained a potential benefit that had not been captured (see section 3.22).

Treatment waning

3.15 The committee noted that the company's scenario capturing the long-term mortality benefit from treating multiple flares with spesolimab assumed no waning of treatment effect over the 16-year period. The committee recalled that spesolimab could be given twice for each flare and some people may have multiple flares per year (see section 3.1). Also, the patient organisation representative highlighted that the age of diagnosis is highly variable, with some flares starting in adolescence. So, some people could have many doses of spesolimab over their lifetime. The committee was concerned that the treatment effect of spesolimab may wane with recurrent use. Clinical experts explained that treatment effect waning is observed in some people who have biological treatments for plaque psoriasis. But this has multiple causes and is not predictable. The committee noted that anti-drug antibodies had been recorded in some people in the Effisayil 1 trial, suggesting treatment waning was plausible. But it agreed that it was not possible to model any effect waning because of the 12-week time horizon. The committee recalled that spesolimab would only be used in clinical practice if the last flare had responded to it (see section 3.12). So, this would reduce the use of spesolimab in cases where waning may occur. The committee concluded that the long-term impact of spesolimab, including any waning of treatment effect, was highly uncertain, and took this uncertainty into account in its decision making.

Inpatient rates

3.16 The company model assumed faster flare resolution with spesolimab, with lower hospitalisation rates. In the company's original model, 77.6% of people who had BAC were assumed to be hospitalised for treatment of GPP flares, based on data from Wolf et al. (2024). The company assumed that only 38.8% of people having spesolimab would be hospitalised. This was based on a company assumption that spesolimab reduced hospital rates by 50%. This was similar to the 48.4%

relative reduction in active flare rates (defined as a GPPGA pustulation subscore of 1 or under) seen in Effisayil 1 compared with the proportion having BAC. At the first committee meeting, 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. But 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. At the first meeting, the committee requested more UK clinical data on inpatient admission rates and duration of stay for GPP flares treated with BAC and spesolimab.

3.17 After consultation, the company explained that it had found no alternative sources of data to accurately calculate the inpatient rates. So, it maintained its preference for inpatient rates based on Wolf et al. (2024). Hospitalisation rates from the Effisayil REP trial (an open-label, single-arm study for spesolimab) suggested the modelled inpatient rate for spesolimab was conservative. Hospital Episode Statistics (HES) data supported the use of Wolf et al. (2024) for the BAC arm. But a stakeholder highlighted that HES data was likely to underestimate the admission rate in the NHS because of poor coding of hospital admissions. The company provided consensus statements by healthcare professionals in the UK, China and the US that supported a 50% reduction in hospital admissions and reduced stay duration with spesolimab. The EAG noted that no data had been provided on the average length of stay in hospital. But, given the lack of alternative data, it updated its base case to align with the company's and provided scenarios varying the percentage reduction of inpatients with spesolimab. The clinical expert stated that the company's assumption was conservative. This is because there is normally a gradual escalation in flare severity before people are admitted to hospital, meaning severe flares can be identified early. So, spesolimab could be given as an outpatient treatment and may stop the flare from escalating to the point of needing hospitalisation. But the committee noted that the relative reduction in admission rates for spesolimab compared with BAC were based on data from the Effisayil 1 trial. It recalled that this included a different population to that seen in the NHS where GPP flares are treated with BAC rather than placebo (see section 3.6). It noted that the Effisayil 1 trial likely overestimated the relative efficacy between spesolimab and

placebo compared with the NHS. So it agreed that a 50% reduction in inpatient rates with spesolimab compared with BAC may be too optimistic. It considered that the trial did support a reduction in inpatient rates and that this was likely to be at least 20% less than that with BAC. The committee concluded that the exact proportion of people with GPP who would be admitted to hospital having spesolimab in the NHS is highly uncertain. But it accepted analyses showing a reduction in hospital admissions of over 20% with spesolimab compared with BAC for decision making.

Intensive care rates

3.18 In its original submission, the company assumed that GPP flares treated with spesolimab never require intensive care admission, whereas some people having BAC would need intensive care admission. The exact proportion is confidential and cannot be reported. Clinical experts at the first meeting explained that it was likely that some GPP flares treated with spesolimab would 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 company did not identify any additional data to inform the intensive care rates for spesolimab or BAC at consultation, so it updated its base case to use the rates from Wolf et al. (2024) for BAC. This aligned with the committee preference at the first meeting. In this, it assumed that 11.5% of people who were hospitalised in the BAC arm ended up in intensive care compared with 5.75% of the spesolimab arm, which is a 50% reduction in rates for spesolimab. The clinical expert at the second meeting stated that this was likely conservative. They anticipated that most people having spesolimab would avoid admission to intensive care because spesolimab is effective at controlling flares, would be given early and starts working quickly. The EAG noted that consensus statements, including one from Japan, supported reduced need for intensive care with spesolimab. But it did not provide data on the proportion of people needing intensive care for GPP flares. But, given the lack of alternative data, the EAG updated its assumption to align with the company's. The committee agreed that the rate of hospitalised people who needed intensive care was highly uncertain. But it accepted the rates from Wolf et al. (2024) for the BAC arm, with a 50% reduction for spesolimab, for decision making.

Hospitalisation costs

3.19 The company model calculated separate costs for people who had treatment in the general ward, in intensive care with or without mechanical ventilation, in day care and as an outpatient. The exact costs for spesolimab and BAC are confidential and cannot be reported here. The committee noted that the company's model estimated a reduction in overall costs, despite significantly higher drug costs. The EAG explained that this was because people whose flares are treated with spesolimab are assumed to have fewer hospital stays, stay in hospital for fewer days and have a lower risk of needing intensive care compared with people having BAC (see section 3.16 and section 3.18). The clinical experts highlighted that there are currently no effective treatments for GPP flares. So people who are admitted to hospital having BAC are likely to stay in longer than those having spesolimab. But, the committee recalled that there was considerable uncertainty about the company's hospitalisation rates because of the short time horizon and lack of available data (see section 3.17). It concluded that the company's costs were very uncertain but acceptable for decision making.

Severity

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

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.21 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ration (ICER) of £20,000 per QALY 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 felt that there were

considerable uncertainties in the company's model, including:

- the treatment effect of spesolimab on people having maintenance biological treatment for plaque psoriasis (see section 3.6)
- whether the short time horizon adequately captured the long-term costs and effects for spesolimab (see section 3.10)
- the proportion of people having BAC and spesolimab who have a subsequent flare in the model (see section 3.13)
- the treatment used for non-response at day 8 for subsequent flares in the spesolimab and BAC arms (see section 3.13)
- whether the treatment effect of spesolimab would wane if used as an acute treatment for multiple flares over a person's lifetime (see section 3.15)
- the rates and costs of hospitalisation for spesolimab and BAC (see section 3.16, section 3.18 and section 3.19).

  It also agreed that the mortality benefit may not have been fully captured (see section 3.14). Because of this, it agreed that the appropriate threshold was around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000) per QALY gained.

Uncaptured benefits

3.22 The committee considered whether there were any uncaptured benefits of spesolimab:

- It recalled that because of the uncertainty around many of the company's assumptions, its preferred analysis did not include a long-term mortality benefit for spesolimab. It agreed the full mortality benefit may not have been captured in the model (see section 3.14).
- The patient organisation representative at the second meeting highlighted that there can be a considerable impact on carers of people with GPP. Providing support during flares can be challenging psychologically, which may negatively impact relationships and family life. The fatigue and pain

associated with a flare can also stop a person with GPP from working, increasing pressure on carers to support the household financially. The committee agreed that the impact of GPP flares on carers may not be captured in the company's model.

- The committee considered that if spesolimab was used to treat a GPP flare, it could reduce the use of biological treatments. At the second meeting, the clinical expert explained that, in people who have a flare treated with spesolimab while on biological treatments, the need for ongoing biological treatments for GPP would be assessed once flare symptoms were under control. But they noted that there was data from Japan to suggest that spesolimab has changed the overall management of GPP. They recalled that some BAC treatments have significant side effects that might be avoided with spesolimab. For example, some biological treatments are associated with a risk of sepsis and ciclosporin can cause chronic renal failure with long-term use. But, the committee also considered that, if used together with biological treatments, spesolimab could increase the risk of adverse effects and that this had not been captured in the model. The committee recalled that there was no data using spesolimab with biological treatments and only 12 weeks of data available from the Effisayil 1 trial (see section 3.4). The committee felt that reducing the use of biological treatments may be an uncaptured benefit of spesolimab, but agreed this was uncertain and not informed by evidence.

  The committee agreed there were potential benefits for spesolimab that had not been fully captured in the company's model. It considered these in its decision making.

Rarity of the condition

3.23 The committee also considered whether the rarity of the condition should be taken into account in decision making. It noted that NICE's manual on health technology evaluations states that evidence generation may be particularly difficult in the case of rare diseases, and allows the committee to make recommendations accepting a higher degree of uncertainty. The committee was aware that GPP is a rare condition. It considered that spesolimab was likely to be

used in an emergency situation, which made it difficult to generate data, especially in a smaller population. But, it recalled that the Effisayil 1 trial was designed with only a 12-week follow up, only recruited 53 people with no UK sites and excluded maintenance biological treatments commonly used in the NHS (see section 3.4). So it would have preferred to see real-world evidence over a longer time period from people with GPP in the UK to support the company's modelled assumptions. The clinical expert highlighted that the heterogeneity in the nature of flares and concomitant treatments for plaque psoriasis made collecting real-world evidence challenging. The committee concluded that it was appropriate to apply some additional flexibility in the amount of uncertainty accepted for decision making because of the challenges in collecting data in the condition. But, it felt that the quality of the evidence could have been improved with further real-world evidence.

Committee's preferred assumptions

3.24 The committee's outlined its preferred assumptions:

- current BAC being ciclosporin and acitretin at first line (week 1) and biological treatments after week 1 (see section 3.3)
- including people with moderate to severe flares, as defined in the Effisayil 1 trial as the population to have treatment for initial flares (see section 3.6)
- SEE exercise used as the most appropriate source to inform the composition and costs of treatments in the BAC arm (see section 3.8)
- treatment response from the Effisayil 1 trial for the spesolimab arm and the Effisayil 1 historical cohort for the BAC arm (see section 3.9)
- a subsequent flare implemented within 12 weeks:
  - in 7.14% of people in the model to align with clinical practice (see section 3.13)
  - defined as a GPPGA pustulation subscore of 2 or more in people whose initial flare had resolved to a GPPGA pustulation subscore of 0 or 1 (see section 3.12)

- no long-term mortality benefit for spesolimab beyond reducing intensive care admissions (see section 3.14)
- Wolf et al. (2024) used for BAC inpatient and intensive care admission rates, with:
  - 77.6% of the BAC arm and at least 62.08% of the spesolimab arm needing inpatient care for flares (at least a 20% reduction in rates for spesolimab; see section 3.16)
  - 11.5% of inpatients having BAC and 5.75% having spesolimab admitted to intensive care (a 50% reduction in rates for spesolimab; see section 3.18)
- using the company's hospital costs, while noting the uncertainty in the estimates (see section 3.19).

Company and EAG cost-effectiveness estimates

3.25 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 ICERs for spesolimab compared with current BAC without spesolimab. After consultation, the company and EAG had the same assumptions in their base cases. The committee noted that spesolimab was dominant over BAC (that is, spesolimab was cheaper and more effective) in the company and EAG base cases. It was also dominant in all scenarios except those assuming a reduction of less than 10% in hospitalisation rates for spesolimab compared with BAC. It recalled that the reduction in hospital admissions with spesolimab was uncertain but likely to be at least 20% compared with BAC (see section 3.16). So, the most plausible scenarios were within the threshold normally considered a cost-effective use of NHS resources. The committee agreed that there was a high level of uncertainty around the company and EAG cost-effectiveness analyses, because of the considerable uncertainty in the clinical and economic evidence (see section 3.21). But, it agreed that it could accept a higher level of uncertainty in this case because of the rarity of the condition and possible uncaptured benefits (see sections 3.22 and section 3.23). So, spesolimab can be used to treat people with GPP flare within the company's modelled population, that is:

- people with initial moderate to severe flares as defined in the Effisayil 1 trial
- people with subsequent flares defined as a GPPGA pustulation subscore of 2 or more, if the last flare was treated with spesolimab and resolved to a GPPGA pustulation subscore 0 or 1.

Other factors

Equality

3.26 Clinical expert opinion at the first meeting 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. But, at the second meeting, the committee noted that the GPPGA total score, used in the definition of an initial flare, included an assessment of redness of skin. It agreed that healthcare professionals should take into account skin colour and how this could affect the GPPGA total score and make the necessary clinical adjustments. Clinical experts confirmed that ethnicity is not a prognostic characteristic. At the second meeting, the committee noted that pregnancy can induce and exacerbate GPP in people with an existing predisposition. The company explained that there was no clinical evidence in people who had GPP in pregnancy, as these people were excluded from the Effisayil 1 trial. But the committee considered that its recommendation included people who develop moderate to severe GPP flares during and after pregnancy if healthcare practitioners consider spesolimab safe to use in these situations. The committee concluded that there are no other equality issues.

Conclusion

Recommendation

3.27 The committee acknowledged the high uncertainty associated with the clinical

evidence and economic modelling for spesolimab. But, it noted that the most plausible cost-effectiveness estimates were within the range normally considered a cost-effective use of NHS resources. So, spesolimab can be used to treat GPP flares as defined within the company's modelled population.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has generalised pustular psoriasis flares and the healthcare professional responsible for their care thinks that spesolimab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

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