OPINION ON MEDICINAL PRODUCTS

anifrolumab
SAPHNELO 300 mg,
solution for dilution for infusion
First assessment

Adopted by the Transparency Committee on 7 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement in addition to standard treatment, for adults with moderate to severe active systemic lupus erythematosus (SLE) with autoantibody presence despite a standard treatment excluding severe active lupus nephritis and severe active central nervous system lupus.

Disapproval of reimbursement for the specific severe active lupus nephritis and severe active central nervous system lupus forms.

Therapeutic improvement?

Therapeutic improvement in patients ineligible for belimumab (moderate SLE forms, contraindication to belimumab) or in the event of failure to respond to belimumab, and having skin involvement.

No therapeutic improvement in patients eligible for belimumab or with no skin involvement.
Role in therapeutic strategy?

The treatments available do not envisage patient recovery, but have the objective of preserving patients' quality of life, and their vital functions during severe episodes, reducing inflammation, preventing complications and limiting the adverse effects of medicinal products in the long term.

While SLE outcomes has improved considerably thanks to early treatment, the disease can still be very severe, and potentially life-threatening, generally on account of kidney or heart involvement. Moreover, on account of its systemic nature and frequent rheumatic and skin involvement, SLE impairs patients’ quality of life in various aspects.

The first-line basic treatment is based on synthetic antimalarials (hydroxychloroquine or chloroquine) which can be associated with low-dose corticosteroids. Immunosuppressant or immunomodulatory drugs [particularly thalidomide (temporary recommendation for use) and methotrexate (off-label)] are used for more severe or more active forms of the disease, poorly controlled by synthetic antimalarials and low-dose corticosteroids, or for forms requiring long-term corticosteroid administration. The choice of treatment depends on the type of involvement and its severity.

Belimumab I.V. treatment is recommended for active forms of systemic lupus, in adults, with autoantibody presence and high disease activity (defined for example by the presence of anti-native DNA antibodies and complement deficiency). It must be used in association with standard treatment, after failure to respond or intolerance to properly observed treatment with synthetic antimalarials, NSAID, corticosteroids and/or immunosuppressants according to the specific involvements. In the absence of data in severe kidney and neurological involvement, it is not recommended to prescribe belimumab in these forms of lupus.

Further medicinal products are used off-label in refractory forms, such as rituximab, systemic tacrolimus, ciclosporin, dapsone, retinoids, thalidomide or lenalidomide.

Role of SAPHNELO (anifrolumab) in the therapeutic strategy:

Considering:
- the evidence of modest efficacy versus placebo:
  - on composite outcome measures (SRI-4 response in the MUSE phase IIb study, not confirmed in the TULIP-1 phase III study, and BICLA response in the TULIP-2 phase III study), in addition to standard treatment, in adults with moderate to severe active systemic lupus erythematosus (SLE) with autoantibody presence despite a standard treatment, who do not have severe active lupus nephritis or severe active central nervous system lupus,
  - and on long-term corticosteroid reduction,
- evidence of efficacy more specifically on severity of skin involvement, but not on joint involvement, the predominant forms of involvement in patients included in studies,
- the lack of evidence of an effect on the frequency of episodes, fatigue and quality of life,
- short-term safety primarily marked by a risk of infection (upper respiratory tract infections, shingles), reactions at the injection side and infusion-related reactions at the start of treatment,
SAPHNELO (anifrolumab) is a second-line treatment, in addition to standard treatment (synthetic antimalarials, corticosteroids, and in the event of failure, immunosuppressants/immunomodulatory drugs include thalidomide, lenalidomide and methotrexate), in patients with moderate to severe active systemic lupus erythematosus (SLE) with autoantibody presence despite well-managed standard treatment. In cutaneous forms failing to respond to standard treatment, SAPHNELO (anifrolumab) represents an alternative to be preferred over thalidomide and lenalidomide which are more poorly tolerated.

No data are available that can be used to position the role of SAPHNELO (anifrolumab) in the therapeutic strategy with respect to BENLYSTA (belimumab), however, based on expert opinion, SAPHNELO (anifrolumab) may also have a benefit as a third-line treatment after failure to respond to belimumab (BENLYSTA).

SAPHNELO (anifrolumab) has no role in the therapeutic strategy for patients with severe active lupus nephritis or severe active central nervous system lupus despite standard treatment in the absence of data from these patients.
Committee’s conclusions

Clinical Benefit

- Systemic lupus erythematosus (SLE) is a proteiform autoimmune disease, primarily affecting women in the period of ovulatory activity (9 women for every 1 man), progressing with episodes of variable severity and which can impair quality of life and is potentially life-threatening.
- SAPHNELO 300 mg (anifrolumab), solution for dilution for infusion is used in the context of symptomatic treatment.
- As additional treatments to standard treatment in adults with moderate to severe active SLE with autoantibody presence despite standard treatment, who do not have severe active lupus nephritis or severe active central nervous system lupus, the efficacy/adverse effect ratio is significant in cutaneous forms considering the evidence of specific efficacy on skin involvement (CLASI) and moderate for other forms.
- A therapeutic alternative is available, BENLYSTA (belimumab), which can be used in patients with high lupus activity despite standard treatment (except for severe central nervous system forms), and in particular, patients with severe lupus nephritis.
- SAPHNELO (anifrolumab) is a second-line or third-line treatment (after failure to respond to belimumab), in addition to standard treatment (see Section 8. Therapeutic strategy). This treatment has no role in the therapeutic strategy for patients with severe active lupus nephritis or severe active central nervous system lupus despite standard treatment in the absence of data from these patients.

→ Public health benefit

Considering:
- the severity of the incapacitating and potentially life-threatening disease and its prevalence
- the partially met medical need,
- the partial response to the identified partially met need on account of:
  - evidence of a modest additional impact on morbidity in terms of reducing disease activity, corticosteroid sparing and reducing skin involvement,
  - the lack of data on severe renal and neurological forms,
  - acceptable short-term safety primarily with non-severe upper respiratory tract infections, shingles, a risk of hypersensitivity reactions and infusion-related reactions at the start of treatment and an unassessed potential long-term risk of onset of serious infections and tumours,
- the lack of evidence of an impact on delivery of care:
  - the lack of expected positive impact on the care and/or life pathway (administration by infusion in a hospital setting, no evidence of an effect in terms of reducing the frequency of episodes and fatigue and in terms of improving quality of life),

SAPHNELO (anifrolumab) is not likely to have an additional impact on public health.
Considering all of these elements, the Committee deems that the actual clinical benefit of SAPHNELO (anifrolumab), solution for dilution for infusion, in addition to standard treatment, in adults with moderate to severe active SLE with autoantibody presence despite standard treatment, who do not have severe active lupus nephritis or severe active central nervous system lupus, is:

- significant for cutaneous forms of SLE,
- moderate for non-cutaneous forms of SLE,

The actual clinical benefit is insufficient in cases of severe active lupus nephritis or severe active central nervous system lupus to justify public funding in view of the alternatives available.

**Clinical Added Value**

Considering:

- the evidence of modest efficacy versus placebo:
  - on composite outcome measures (SRI-4 response in the MUSE phase IIb study, not confirmed in the TULIP-1 phase III study, and BICLA response in the TULIP-2 phase III study), in addition to standard treatment, in adults with moderate to severe active systemic lupus erythematosus (SLE) with autoantibody presence despite a standard treatment, who do not have severe active lupus nephritis or severe active central nervous system lupus,
  - and on long-term corticosteroid reduction in patients receiving ≥ 10 mg/day of prednisone or equivalent at inclusion,
- evidence of efficacy versus placebo more specifically on severity of skin involvement (predominant form of involvement in patients included in studies),
- acceptable short-term safety primarily marked by a risk of infection (upper respiratory tract infections, bronchitis, and shingles), reactions at the injection side and infusion-related reactions at the start of treatment,

but:

- the lack of evidence of an effect on joint involvement which was also a predominant form of involvement in patients included in studies,
- the lack of evidence of an effect on the frequency of episodes, fatigue and quality of life, which are relevant outcome measures in SLE,
- the lack of robust data versus belimumab (BENLYSTA),
- the lack of long-term safety data making it possible to assess the risk of serious infections and the cancer risk,

SAPHNELO (anifrolumab), solution for dilution for infusion, in addition to standard treatment, in adults with moderate to severe active SLE with autoantibody presence despite standard treatment, who do not have lupus nephritis or severe active central nervous system lupus:

- provides minor clinical added value (CAV IV) in the therapeutic strategy for cutaneous forms in patients ineligible for belimumab or in the event of failure to respond to belimumab;
- provides no clinical added value (CAV V) in the therapeutic strategy in patients eligibles for belimumab or with no skin involvement.