OPINION ON MEDICINAL PRODUCTS

Ciclosporin
IKERVIS 1 mg/mL

Eye drops, emulsion

First assessment

Adopted by the Transparency Committee on 31 August 2022

SUMMARY

The legally binding text is the original French opinion version

- **Severe keratitis**
- **Sectors: Community and Hospital**

Key points

Disapproval of reimbursement for the treatment of severe keratitis among adult patients presenting with dry eyes failing to resolve despite the instillation of artificial tears.

Role in therapeutic strategy?

The usual initial treatment of dry eye syndrome, regardless of cause, is based on:

- correcting contributing factors, wherever possible (medicinal products, environmental factors, eye drops containing preservatives, in particular quaternary ammoniums);
- and tear replacement therapy (artificial tears in the form of eye drops, gels, as well as viscoelastic solution medical devices used after the first two have failed).

After failure to respond to tear replacement therapy, several therapeutic options are used according to the degree of severity of the dry eye syndrome, its cause, and patient characteristics. The recommendations proposed by the *International Dry Eye Workshop* in 2017 particularly include:

➔ **Step 1:**
- Education and dietary and environmental modifications, including potential elimination of offending systemic and topical medications,
- Ocular lubricants (artificial tears) of various types,
- Lid hygiene and compresses of various types.

➔ **Step 2:** if Step 1 options are inadequate, add:
- Anti-inflammatory drugs including topical cyclosporin and limited-duration topical corticosteroids,
- Tetracyclines (meibomitis, rosacea),
- Punctal occlusion,
- Topical secretagogues (e.g. rebamipide and diquafosol; not available in France),
- Moisture chamber spectacles/goggles.

➔ **Step 3:** if Step 2 options are inadequate, add:
- Oral secretagogues (e.g. pilocarpin)
- Autologous serum,
- Contact lenses/scleral lenses.

➔ **Step 4:** if Step 3 options are inadequate, add:
- Topical corticosteroids for longer duration (off-label),
- Permanent punctal occlusion,
- Surgery (including amniotic membrane grafts),

These recommendations may be adapted by practitioners according to their personal clinical experience and each patient's individual profile.

The Committee reiterates that, in the case of long-term use, the preservatives contained in eye drops may cause adverse inflammatory conjunctival effects and ocular surface toxicity, and hence preservative-free eye drops should be preferred.

Role of IKERVIS (ciclosporin) in the therapeutic strategy:

Considering:

- the lack of evidence, in the studies previous assessed (SANSIKA and SICCANOVE) of any superiority of IKERVIS (ciclosporin) versus placebo in patients with severe keratitis associated with dry eye syndrome failing to resolve despite the instillation of artificial tears.

- the new non-comparative data from phase 1 of the post-marketing study, which do not provide a basis to reach a conclusion on the efficacy of IKERVIS (ciclosporin) versus placebo in this patient cohort,
- the lack of availability of findings from phase 2 (comparative versus placebo) of this study (scheduled for 2023),

IKERVIS (ciclosporin) has no role in the therapeutic strategy for the management of severe keratitis among adult patients presenting with dry eyes failing to resolve despite the instillation of artificial tears.

Committee's conclusions

Actual Clinical Benefit

- Severe keratitis with dry eyes is a painful condition impairing quality of life, and potentially ultimately resulting in blindness.

- The proprietary medicinal product IKERVIS 1 mg/ml (ciclosporin), eye drops, is a curative medicinal product.

- Based on the current data available, failing clinical data demonstrating the superiority of IKERVIS (ciclosporin) versus placebo, the efficacy/adverse effect ratio is not established for the treatment of severe keratitis in adult patients presenting with dry eyes failing to resolve despite the instillation of artificial tears. It should be noted that the Committee was awaiting the data from the post-marketing study required by the EMA, with the endpoint of demonstrating the superiority of ciclosporin versus placebo in the longer term (24 months instead of 6 months in the SANSIKA study). However, only the findings of the non-comparative phase 1 of the study are available at the present time, and the primary outcome measure of this phase (correlation between the average trend in the CFS score and the symptom score based on the SANDE questionnaire) is not suitable for demonstrating the clinical benefit of IKERVIS (ciclosporin). The findings of phase 2 of the study comparing the efficacy IKERVIS (ciclosporin) versus placebo are not available to date (scheduled for 2023).

- Therapeutic alternatives are available, particularly hospital-prepared ciclosporin.

- IKERVIS (ciclosporin) has no role in the therapeutic strategy for the management of severe keratitis among adult patients presenting with dry eyes failing to resolve despite the instillation of artificial tears (see Section 09. Role in therapeutic strategy).

➔ Public health benefit

Considering:

- the severity of the disease which substantially impairs quality of life, and may ultimately result in blindness, and that the prevalence of dry eye syndrome varies from 5 to 15% in Europe.
- the identified partially met medical need,
- the lack of additional response to the identified partially met medical need in view of the lack of clinical data providing a basis to reach a conclusion on the efficacy of IKERVIS (ciclosporin) versus placebo, and demonstrate an additional impact on morbidity,
- the lack of robust data on a potential impact on the patient's care and life pathway and on quality of life,

IKERVIS (ciclosporin) 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 IKERVIS 1 mg/ml (ciclosporin), eye drops in emulsion is insufficient for the marketing authorisation indication to justify public funding in view of the alternatives available.

The Committee disapproves inclusion in in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for the indication and at the dosages of the marketing authorisation.