I.9 Prednisolone – infantile spasm – EML

Reviewer summary

☒ Supportive of the proposal

☐ Not supportive of the proposal

Justification (based on considerations of the dimensions described below):

- **Public health relevance**
  Infantile epileptic spasms syndrome (IESS) is a severe epilepsy syndrome that is **characterized by infantile spasms and developmental regression. T**he estimated incidence of IESS is 30/100,000 live births, and accounts for ~10% of epilepsies that begin prior to 3-years-old. **Prompt treatment with appropriate first-line therapies can improve outcomes long-term developmental and cognitive outcomes**. Poorer developmental outcomes in IESS appear to be most related to lags in treatment initiation
- **Evidence of comparative efficacy and safety**
  1. Hormonal treatment (**oral prednisolone** or ACTH) or nonhormonal treatment (vigabatrin) are internationally well-accepted first-line treatment options.
  2. Six SR/meta-analysis assessed treatment options for IESS, with either the three first-line treatments (prednisolone, ACTH, +/- vigabatrin) against each other, or with first-line treatments against second-line therapies. **Strong evidence showed the use of high-dose oral prednisolone as more efficacious or non-inferior, equally safe**, and **more cost-effective treatment** for IESS in comparison to the other first-line therapies of ACTH and vigabatrin, and superior to other non-standard treatments with alternative anti-seizure medications, **with the exception of IESS secondary to TSC** (tuberous sclerosis complex) which tend to respond better to vigabatrin. **Acute adverse reactions amongst all three first-line therapies are similar.**
  3. Corticosteroids carry risks that require careful management. The safety concerns include impact of long-term use on endocrine function, potentially leading to adrenal insufficiency upon withdrawal, infection risk, impact on cardiovascular and renal function, increased irritability and poorer sleep, bone density, Ophthalmic complications in children
- **Cost and cost-effectiveness considerations**
  1. While efficacy and side-effect profile may be similar, there is a **marked cost difference between prednisolone and other first-line therapies** – with **prednisolone having a significant lower cost,** making it more feasible and accessible to implement as a therapy for IESS on an international scale.
  2. Studies suggests that **high dose oral prednisolone regimens are significantly more cost-effective.**
- **Any other issues that may be relevant in determining the status of a medicine as 'essential' (e.g., recommendations in WHO guidelines, feasibility of use, diagnostic requirements, availability, access).**
  1. Prednisolone and IESS is currently **not covered in WHO guidelines.**
  2. **Twelve treatment guidelines** from different parts of the world **recommend either hormonal therapy (prednisolone, ACTH) and/or vigabatrin as first-line therapies**.
  3. Oral prednisolone is **available in liquid and tablet formulations** for use in IESS. **Studies suggests that high dose oral prednisolone regimens are easier for administration, are more widely available.**
  4. **Prednisolone** is **approved for use** across stringent regulatory agencies **across the world.**
  5. **Prednisolone is available in multiple generic forms** and is **widely available in countries.**
  6. **Prednisolone** is included in **131 out of 137 national essential medicines lists**, which has been key to improve i**ts availability and affordability.**

Recommendation: The strong body of evidence has shown that **early treatment with the first-line oral prednisolone is associated with better epilepsy and neurodevelopmental outcomes**. Findings from systematic reviews and meta-analysis suggest that hormonal therapies have higher efficacy than vigabatrin in the non-Tuberous Sclerosis Complex (TSC) IESS population. Numerous network meta-analyses and head-to-head trials have found that **relative to other hormonal therapies** (ACTH injections), **prednisolone has been found to be equivocal (or superior) in efficacy, similar in side effect profile, and significantly more cost-effective.** IESS is not currently included as an indication on the EMLc, and no IESS-specific therapy is approved. **Timely and effective treatment is vital** for the

	improvement of clinical outcomes. Thus, I highly recommend **listing prednisolone as an individual medicine for IESS under the subsection for antiseizure medicines (subsection 5.1), with a specific indication for non-TSC epilepsy condition of IESS.** Meanwhile, ***[c]*** **symbol is placed next to prednisolone on the complementary list to** restrict its use for specific indication for non-TSC IESS and emphasize special requirements for specialist medical care, high-dose regimen, and adverse effect monitoring. Adding **a new specific indication for prednisolone for IESS on the EMLc under antiseizure treatments with a specific indication for IESS can improve** awareness of the condition and **access to treatment for IESS,** and help **ensure appropriate, timely treatment**, which would have a large impact on the prognosis and long-term sequalae in children with IESS.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;)	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) Baseline testing with full blood count, electrolytes, glucose, creatinine and urea, urinalysis, weight, and blood pressure should be performed. Screening for risk of tuberculosis should be performed; if high risk area, chest x-ray should be considered. Guidelines recommend weekly blood pressure and urine monitoring during course at minimum, if feasible, weekly laboratory studies with electrolytes and blood counts is also often recommended. Some guidelines also recommend weekly weights for monitoring. Fevers (>38.5°C) warrant immediate evaluation given higher risk of infection while on treatment.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☐ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ Yes ☐ No ☐ Not applicable

Does the medicine have wide regulatory approval?	☒ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable