Expert peer review on application for Polyvalent Human Immunoglobulins 20% for subcutaneous administration

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      No. We have added other six studies on efficacy. Please see attachment part 1.
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      SCIG 20% maintained or improved serum IgG levels without dose increases and effectively protected patients with PID against infections in adults and children previously treated with IVIG or SCIG 16%. But there is no evidence to tell whether SCIG 20% has better efficacy than SCIG 16% and SCIG 15% which have been listed in EML
   c. Please provide any additional relevant information with reference
      We find 6 other studies that reported the efficacy of SCIG 20%, and concluded that it has good efficacy for patients with PID, especially on improving HRQL score and overall treatment satisfaction than IVIG.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      No. We find three other studies on safety. Please see attachment part 1
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      The majority of adverse events associated with SCIG 20% are mild or moderate in adults and children, and comparative studies concluded that safety of SCIG 20% was not inferior to SCIG 16%, but no evidence showing that SCIG 20% has better safety than two other SCIG in EML.
   c. Please provide any additional relevant information with reference
      We find three other studies which reported SCIG 20% has good safety in adults and children, and in which one concluded that SCIG 20% is safe for children under 2 years old although it is not licensed in this age group.

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      No. See attachment part 1
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      The applicant failed to provide any data on the cost of SCIG 20%.
   c. Please provide any additional relevant information with reference
When patients switch from IVIG therapy to SCIG 20%, dose adjustment requirements would increase overall drug utilization and cost. But there is no study to compare the cost effectiveness between SCIG 20% and other SCIG.

d. Is the product available in several low and middle income countries?

SCIG 20% has not yet been registered in China. As far as we know it has been only available in some high income countries like USA and European countries, and we did not find any relevant data on this product in other low and middle income countries.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

There is no data about primary immunodeficiency in “Health Statistics Yearbook 2011” of China, in which only one summarized data for D50-D89. We find in the global, about 1 in 500 people is born with a primary immunodeficiency. And in the United States, as many as 500,000 people have primary immunodeficiency, with about 50,000 cases diagnosed each year. The life-long human immunoglobulin replacement therapy is essential for individuals with primary immune deficiencies.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

No. Five guidelines from three countries (UK, Canada, USA) recommend SCIG, but no one has recommended SCIG 20%.

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

Yes. Trough levels of IgG should be measured and assessed in conjunction with the patient’s clinical response. User should be instructed in infusion techniques.

6. Is the proposed product registered by a stringent regulatory authority?

No

7. Any other comments

It is unclear whether SCIG 20% has better efficacy, safety or cost-effectiveness compared with other SCIG formulations listed in EML and EMLc, as lack of evidence. However, some of the studies found by us are only available in abstract. The conclusion may be changed if the full texts are retrieved.

8. What is your recommendation to the committee (please provide the rationale)

Based on existing evidence, we do not recommend this product to be included in EML or EMLc. Both the application document and our review results fail to conclude that SCIG 20% has any obvious advantages on efficacy, safety and cost-effectiveness compared with other SCIG formulations listed in EML and EMLc. Further comparative studies are needed to assess the efficacy, safety and cost-effectiveness of SCIG 20% before it can be considered into EML or EMLc.
## Comparative results between the applicant and reviewer’s data

### 1. Studies included

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<thead>
<tr>
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<th>Applicant</th>
<th>Reviewer</th>
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<tr>
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<td><strong>Cost</strong></td>
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<td><strong>2. Review results</strong></td>
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### Infection

- **Efficacy**
  - Adults and children: SBI: 0-0.06/year/patient
  - All infections: 2.4-5.18/year/patient
  - SCIG 20% can effectively protect patients against infections in children and adults previously treated with IVIG or SCIG 16%.

### HRQL

- **Efficacy**
  - Adults and children: HRQL score: IVIG 53.7 vs SCIG 20% 71.5
  - SCIG 20% Patients treated with IgPro20 has a good HRQL score and overall treatment satisfaction in children and adults.

### Mean serum IgG level

- **Efficacy**
  - Adults and children: Mean (±SD) serum IgG levels: IVIG 6.51±1.32 g/L vs SCIG 20% 7.28±1.47 g/L.
  - IgG levels: SCIG 20% were similar to SCIG 16% and higher by 17.7% than IVIG.

### Safety

- **ADR**
  - Adults and children: 99% of AEs were mild or moderate. No serious, SCIG 20% related ADR were reported
  - Nearly all the adverse events caused by SCIG 20% were mild or moderate both in children and adults.

### Applicability

- **Cost**
  - It would increase overall drug cost, when patients switched from IGIV therapy to IGSC 20%.
  - It caused additional cost of $25,000/patient/year, when patients switched from IGIV to SCIG 20%.
<table>
<thead>
<tr>
<th>3. Level of evidence</th>
<th>2b*</th>
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<tr>
<td>4. Conclusion and recommendation</td>
<td>We do not recommend the SCIG 20% to be included in EML or EMLc, as no evidence shows that SCIG 20% has any obvious advantages on efficacy, safety and cost-effectiveness compared with other SCIG formulations listed in EML and EMLc.</td>
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NR: Not reported; SBI: Serious bacterial infection
* We regard before after studies (historical controlled) as level of 2b evidence according to evidence grading system developed by Oxford Evidence Based Center in 2001.