Proposal for the inclusion of PEG-E coli asparaginase in the WHO Model list of ESSENTIAL MEDICINES for the treatment of acute lymphoblastic leukemia.

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1. Name of the focal point in WHO submitting or supporting the application
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2. Name of the organization(s) consulted and/or supporting the application
   International Pediatric Oncology Society (SIOP)

3. International Nonproprietary Name (INN, generic name) of the medicine
   3.1 PEGylated Escherichia coli asparaginase (Oncaspar™ and approved high-quality biosimilars)

4. Formulation proposed for inclusion; including adult and pediatric (if appropriate)
   1.1 PEGylated Escherichia coli asparaginase (pegaspargase (Oncaspar™) and approved high-quality biosimilars) is supplied in vials containing 3750 units and used at doses of 1000-2500 U/m² as part of multi-agent protocols.
   4.1 International availability
   4.1.1 Servier is the major produce of the originator branded pegaspargase (Oncaspar). Locally-produced biosimilars are available in China and India.

5. Approvals by major regulatory agencies
   5.1 Pegasparagase (Oncaspar)
      5.1.1 The U.S. Food and Drug Administration (FDA) approved pegaspargase (Oncaspar) in 1994 for relapsed ALL and in 2017 for newly diagnosed patients, in combination with multi-agent chemotherapy regimens.
      5.1.2 The European Commission has granted marketing authorization for Oncaspar and it is available in almost all high-income countries and many upper middle-income countries.
      5.1.3 Biosimilar versions are available from suppliers in several countries.
6. Whether listing is requested as an individual medicine or as an example of a therapeutic group?

Asparaginases represent a therapeutic group including native E coli asparaginase, PEGylated E coli asparaginase, Erwinia asparaginase, and biosimilars. When asparaginases are used at the recommended dose and schedule and when use is not limited by hypersensitivity or neutralizing antibodies, any of these 3 asparaginases effectively treat ALL. The ideal situation is to have PEGylated E coli asparaginase as frontline therapy followed by Erwinia asparaginase for second-line use if hypersensitivity or neutralizing antibodies develop to pegasparagase. However, Erwinia asparaginase is not available in many countries, so minimizing the risk of hypersensitivity to frontline asparaginase is imperative in these settings to assure that patients receive all doses needed.

7. Treatment details (requirements for diagnosis, treatment and monitoring)

7.1 Diagnosis and risk stratification of patients with ALL depends on the presenting white blood cell count, age, immunophenotype, and cytogenetics at presentation, and on the quantity of minimal residual disease (MRD) present at the end of remission induction therapy. Four-color flow cytometry with a suitable panel of markers is sufficient for risk stratification and MRD testing in most cases.

7.2 Treatment regimens for ALL include remission induction, consolidation, and continuation therapy, which differ for low- intermediate- and high-risk patients. However, all 3 groups can be cured with modern treatment regimens that include high-quality asparaginase and when the patient is able to receive all doses of asparaginase needed for their risk group.

7.3 Monitoring of patients for complete response (by morphology) and minimal residual disease response (by flow cytometry or PCR) at the end of remission induction establishes that the patient has attained a deep remission and does not require intensification of therapy. If minimal residual disease levels are high, then patients should switch to a higher-risk group and receive the more intense chemotherapy necessary to optimize cure rates for higher-risk patients. Higher-risk patients require protocols with more intense treatment, including more doses of asparaginase.

Importance of asparaginase

Acute lymphoblastic leukemia (ALL) affects 120,000 people each year worldwide, including children and adults. It can be permanently cured more than 80% of the time with treatment regimens that combine glucocorticoids, anthracyclines, vincristine, mercaptopurine, and asparaginase. Extensive clinical data support the use of asparaginase therapy in pediatric acute lymphoblastic leukemia (ALL) and the benefit of intensive asparaginase treatment compared with less intensive regimens has been demonstrated (Figure 1). It is also a key component of therapy for relapsed ALL. The three most-used formulations include Esherichia coli asparaginase (Elspar, Leunase, Kidrolase, and others), PEGylated-Esherichia coli asparaginase (Oncaspar), and Erwinia asparaginase (Erwinaze), as a second-line asparaginase for patients who
develop hypersensitivity to *E coli* asparaginases. In high-income countries, PEG-*E. coli* asparaginase is used as frontline therapy because it is long-acting and has a much lower rate of hypersensitivity and silent neutralizing antibody formation than native *E coli* asparaginase.

Figure 1. Improved event-free survival when more intensive asparaginase therapy is used\(^\text{12}\)

Allergic reactions can limit the ability to complete asparaginase therapy
Native *E coli* asparaginase is on the WHO list of essential medications, but allergic reactions to *E. coli* asparaginase occur in 20% to 42% of patients with ALL, and silent (asymptomatic) neutralizing antibody formation to another 30-40%, such that 2/3 of patients do not complete all their required asparaginase unless they have access to a second asparaginase product, usually Erwinia asparaginase.\(^\text{13-21}\) Hypersensitivity or silent antibody formation necessitate a change to another form of asparaginase. Unfortunately, the supply of Erwinia asparaginase has been limited to high-income countries, and even there is insufficient to meet the needs of patients who react to their frontline asparaginase. PEG-asparaginase is associated with much lower reaction rates (10-15%) and lower incidence of neutralizing antibodies (1%).\(^\text{13-15,22,23}\) When no second product is available (or an allergy occurs to the alternate asparaginase), the inability to complete asparaginase treatment increases the risk of relapse, which is associated with poor prognosis, with survival after relapse ranging from 20% to 50% (Figure 2). Furthermore, relapse therapy entails intense salvage chemotherapy followed by allogeneic stem cell transplantation, which imposes high additional costs of treatment ($100,000 to $200,000 US dollars in most of South America; $800,000 to $1,000,000 in the US). Even when a substitute asparaginase product is available (e.g. Erwinaze), the costs of treatment increase enormously.\(^\text{20}\) Therefore, minimization of allergic reactions to the initial form of asparaginase improves outcomes and reduces costs.

**PEG-*E coli* asparaginase frontline**
PEGylation of *E coli* asparaginase to create PEG-*E. coli* asparaginase was undertaken to increase the half-life of asparaginase and decrease immunogenicity and allergic reactions/antibody formation from 20-42% to 2-11% (Table 1)\(^\text{12}\) Most encouraging, the recently published UKALL 2003 trial used PEG-*E. coli* asparaginase in a schedule that included several days of glucocorticoids prior to each dose of PEG-*E. coli* asparaginase in the lower-risk and
intermediate-risk patients, who had a 1% rate of allergic reaction and excellent event-free survival.\(^{24}\) Patients on the higher-risk arm received several doses of PEG-\textit{E. coli} asparaginase without preceding glucocorticoids and had a reaction rate of 6%, such that in the whole study the reaction rate was 2%.\(^{24,25}\) This has led to an immediate change in practice, and modification of existing protocols to include glucocorticoids a couple of days before each Oncaspar dose, in the hope of reducing allergic reactions to 1%, thus allowing patients to complete all asparaginase and reducing the need for a second-line asparaginase (e.g. Erwinia).

Table 1. Addition of PEG to the asparaginase molecule protects it from the immune system and reduces antibody formation from 20-42% to 2-11%\(^{12}\)

<table>
<thead>
<tr>
<th>Asparaginase Type</th>
<th>Dose</th>
<th>Concomitant Steroid Medications</th>
<th>Antibody-Positive Patients</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{E. coli}</td>
<td>10 000 IU/m(^2) IM 3x/wk for 9 doses during induction and 9 during reinduction</td>
<td>Prednisolone</td>
<td>35.5%</td>
<td>\textit{Woo 2000}(^{46})</td>
</tr>
<tr>
<td>PEG</td>
<td>2500 IU/m(^2) IM for a total of 4 doses (induction) and 1 dose (intensification)</td>
<td>Prednisolone/dexamethasone</td>
<td>26-42%</td>
<td>Avramis 2002(^{28})</td>
</tr>
<tr>
<td>Erwinaze</td>
<td>2000 IU/m(^2) IV or IM daily for a total of 10 doses (induction), 2x/wk for a total of 4 doses (reinduction)</td>
<td>Dexamethasone</td>
<td>11%</td>
<td>\textit{Hawkins 2004}(^{48})</td>
</tr>
<tr>
<td></td>
<td>2000 IU/m(^2) IV or IM daily for a total of 10 doses (induction), 2x/wk for a total of 4 doses (reinduction)</td>
<td>Prednisolone/dexamethasone</td>
<td>11%</td>
<td>\textit{Avramis 2002}(^{29})</td>
</tr>
</tbody>
</table>

\textit{E. coli} indicates \textit{Escherichia coli}; IM, intramuscular; SC, subcutaneous; PEG, polyethylene glycol; IV, intravenous.

\textbf{Dose equivalence of different asparaginase products}
Asparaginase products have different molecular structures, different half-lives, and different clinical activities per unit (see Table 2 for conversions between products). Since PEG-\textit{E. coli} asparaginase is 6 to 9 times more potent than native \textit{E. coli} asparaginase and each dose lasts 2-3 weeks instead of 2-3 days, modern ALL protocols require lower doses and fewer doses of PEG-\textit{E. coli} asparaginase to provide the asparaginase needed for the patients (Table 3). Indeed, the 2500 U/m\(^2\) dose approved in the USA has sufficient asparaginase activity to last 3 to 6 weeks,\(^{26}\) such that doses of 1000 to 1500 U/m\(^2\) are used in many protocols in other countries.\(^{27-30}\)

Table 2. Sources and characteristics of different asparaginases

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Bacterial Source</th>
<th>Pharma Company</th>
<th>Half-life</th>
<th>Equivalent dose</th>
<th>Conventional dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erwinaze</td>
<td>Erwinia</td>
<td>Jazz</td>
<td>16 hours</td>
<td>20,000</td>
<td>10000-20000 U/m(^2) 3x weekly</td>
</tr>
<tr>
<td>Elspar</td>
<td>\textit{E. coli}</td>
<td>Merck</td>
<td>26-30 hours</td>
<td>10,000</td>
<td>6000-10000 U/m(^2) 3x weekly</td>
</tr>
<tr>
<td>Leunase</td>
<td>\textit{E. coli}</td>
<td>Medac</td>
<td></td>
<td>5,000</td>
<td>6000 U/m(^2) 3x weekly</td>
</tr>
<tr>
<td>Oncaspar</td>
<td>PEG \textit{E. coli}</td>
<td>Servier</td>
<td>5.5-7 days</td>
<td>300-500</td>
<td>1000 to 2500 U/m(^2) q 2-3 weeks</td>
</tr>
</tbody>
</table>
Asparaginase options for patients – 3 possible strategies for frontline, second-line, and third-line asparaginase use

1. Native *E coli* asparaginase → hypersensitivity or neutralizing antibodies → no further asparaginase
2. Native *E coli* asparaginase → hypersensitivity or neutralizing antibodies → PEG-*E coli* asparaginase
3. Native *E coli* asparaginase → hypersensitivity or neutralizing antibodies → *Erwinia* asparaginase
4. PEG-*E coli* asparaginase → hypersensitivity or neutralizing antibodies → no further asparaginase
5. PEG-*E coli* asparaginase → hypersensitivity or neutralizing antibodies → *Erwinia* asparaginase

The least effective and least cost-effective of these 5 strategies is #1, which is the most common scenario in low- and middle-income countries (LMIC), where often neither PEG-*E coli* asparaginase nor *Erwinia* asparaginase are available. Strategies using PEG-*E coli* asparaginase as initial therapy are more effective because they reduce the rates of hypersensitivity and neutralizing antibodies from a total of 50-65% (including both) to 10-15% (including both) and thus allow many more patients to continue their initial asparaginase and complete all doses. Completion of all doses of frontline asparaginase reduces the risk of relapse and thus greatly reduces costs (since salvage therapy is very expensive). It also reduces the need for second-line *Erwinia* asparaginase, which is not available in many countries (especially LMIC) and which has suffered from recurrent shortages and stock-outs even in high-income countries (HIC).

Strategy #4 has been proposed as an alternative to #5 because of the high cost of *Erwinia* asparaginase, but strategy #5 is more effective and cost-effective because completing all needed asparaginase reduces the risk of relapse by 10-17% and thus saves the costs of salvage therapy, allogeneic bone marrow transplantation, and long-term morbidity from these intense therapies. Therefore, the most effective and cost-effective strategy is upfront use of PEG-*E coli* asparaginase followed by *Erwinia* asparaginase, when available, in the 10-15% of patients who develop hypersensitivity.

Figure 2. Long duration of action of Oncaspar (gold line)\textsuperscript{26}
The green line represents the desirable level of asparaginase activity. The average patient who receives Oncaspar 2500 U/m² has adequate asparaginase activity for 24 days, a duration that would require repeated dosing of native E coli asparaginase 2-3 times per week during this interval, or a total of 6 to 9 doses, to achieve comparable asparaginase activity.13,26

8. Information supporting the public health relevance.

Epidemiology of acute lymphoblastic leukemia in children and adults
Acute lymphoblastic leukemia (ALL) affects 120,000 people each year worldwide, including children and adults.

Curability of acute lymphoblastic leukemia
Acute lymphoblastic leukemia can be permanently cured more than 80% of the time with treatment regimens that combine glucocorticoids, anthracyclines, vincristine, mercaptopurine, and asparaginase. Extensive clinical data support the use of asparaginase therapy in pediatric acute lymphoblastic leukemia (ALL) and the benefit of intensive asparaginase treatment compared with less intensive regimens has been demonstrated (Figure 1).1-7 It is also a key component of therapy for relapsed ALL.5-10

9. PEGylated asparaginase and Erwinia asparaginase for acute lymphoblastic leukemia
Asparaginases are essential components of the multi-drug regimens needed to cure ALL, but must be used as multiple doses over several phases of therapy, and combined with other chemotherapeutic agents as part of a comprehensive protocol to achieve best results (Table 3). Suitable concomitant chemotherapy (e.g. anthracyclines, vincristine, methotrexate) is already listed on the EML.

Table 3. Substitution of PEG-E coli asparaginase for native E coli asparaginase in a typical protocol for acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>ALL risk group</th>
<th>Treatment phase</th>
<th>Native E coli asparaginase (units/m²)</th>
<th>PEG-E coli asparaginase (units/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lineage, low risk</td>
<td>Induction</td>
<td>5000 days 12, 15, 18, 21, 24, 27, 30, 33</td>
<td>1000 day 12</td>
</tr>
<tr>
<td></td>
<td>Late consolidation</td>
<td>5000 days 10, 12, 14, 16</td>
<td>1000 day 4</td>
</tr>
<tr>
<td>B-lineage, high risk</td>
<td>Induction</td>
<td>10000 days 8, 11, 14, 17, 20, 23, 26, 29, 32</td>
<td>1000-2500 day 8</td>
</tr>
<tr>
<td></td>
<td>Intensification</td>
<td>6000 days 1, 3, 5, 8, 10, 12</td>
<td>1000-2500 day 4</td>
</tr>
<tr>
<td></td>
<td>Interphase</td>
<td>10000 days 2, 23, 44</td>
<td>1000-2500 day 4</td>
</tr>
<tr>
<td></td>
<td>Late consolidation</td>
<td>6000 days 1, 3, 5, 8, 10, 12</td>
<td>1000-2500 day 4</td>
</tr>
<tr>
<td>T-cell</td>
<td>Induction</td>
<td>10000 days 14, 16, 18, 20, 22, 24, 26, 28, 30</td>
<td>1000-2500 day 14</td>
</tr>
<tr>
<td></td>
<td>Intensification</td>
<td>6000 days 1, 3, 5, 8, 10, 12</td>
<td>1000-2500 day 4</td>
</tr>
<tr>
<td></td>
<td>Interphase</td>
<td>10000 days 2, 23, 44</td>
<td>1000-2500 day 24</td>
</tr>
<tr>
<td></td>
<td>Late consolidation</td>
<td>6000 days 1, 3, 5, 8, 10, 12</td>
<td>1000-2500 day 4</td>
</tr>
</tbody>
</table>

All numbers represent international units/m² of body surface area. * Although the dose-equivalence of native to PEGylated E coli asparaginase is 24-36:1, standard doses of PEG-E coli asparaginase most commonly used in published protocols are 1000 U/m², 1500 U/m² and 2500 U/m².
10. Summary of comparative effectiveness in a variety of clinical settings:

PEGylated E coli asparaginase is widely used around the world and is recommended as frontline therapy for children, adolescents, and young adults by NCCN guidelines and national guidelines of many countries.\textsuperscript{31}

11. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group

\textit{Cost comparison of Native E. coli asparaginase versus PEG-E. coli asparaginase}

Table 4 summarizes the number of doses of native or PEG-E coli asparaginase needed for patients treated on a typical BFM-based protocol. Native \textit{E coli} asparaginase is available in vials of 10000 units each, so patients whose body surface area is \(\leq 1\) m\(^2\) and whose dose of asparaginase is 10000 units/m\(^2\) need only 1 vial. On the other hand, patients whose body surface area is more than 1 m\(^2\) will need 2 vials per dose, and any unused native \textit{E coli} asparaginase in the second vial is often wasted (unless another patient is being treated on the same day). PEG-\textit{E coli} asparaginase is available in vials of 3750 units each, and is dosed at 1000-2500 units/m\(^2\) such that almost all patients require only 1 vial.

Average body surface area (BSA) values for children of various ages, men, and women are:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>BSA (m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (newborn)</td>
<td>0.25</td>
</tr>
<tr>
<td>Child of 2 years</td>
<td>0.5</td>
</tr>
<tr>
<td>9 years</td>
<td>1.07</td>
</tr>
<tr>
<td>10 years</td>
<td>1.14</td>
</tr>
<tr>
<td>12-13 years</td>
<td>1.33</td>
</tr>
<tr>
<td>Women</td>
<td>1.6</td>
</tr>
<tr>
<td>Men</td>
<td>1.9</td>
</tr>
</tbody>
</table>

In pediatric protocols, approximately 75\% of patients are 0 to 10 years old and 25\% are older than 10 years.\textsuperscript{6} Based on the age distribution of children with ALL and the distribution of body surface area by age, the following assumptions are made for the cost-effectiveness calculations (Table 4).

About 27.5\% of patients who require asparaginase will be children whose body surface area is 1 m\(^2\) or less and who therefore require only 1 vial of native \textit{E coli} asparaginase 10,000 U per dose. These patients receive 6 doses of native \textit{E coli} asparaginase 10,000 U/m\(^2\) or if they have access to PEG-\textit{E coli} asparaginase they receive up to a single vial (3750 U) to achieve a dose of 1000 to 2500 U/m\(^2\). For older children and adults (72.5\% of people with ALL), 12 vials of native \textit{E coli} asparaginase are needed (2 vials per dose x 6 doses) or PEG-\textit{E coli} asparaginase single vial (3750 U).
Table 4. Distribution of body surface area (BSA) by age in patients with acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Patient group</th>
<th>BSA &lt; 1 m²</th>
<th>BSA 1-1.5 m²</th>
<th>BSA &gt; 1.5 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 0-10 years</td>
<td>37.5%</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Children 11-19 years</td>
<td>12.5%</td>
<td>10%</td>
<td>70%</td>
</tr>
<tr>
<td>Adult women</td>
<td>25%</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>Adult men</td>
<td>25%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>BSA distribution of all patients combined</td>
<td>27.5%</td>
<td>32.5%</td>
<td>40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vials needed per dose</th>
<th>Native E coli</th>
<th>PEG-E coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses during remission induction</td>
<td>6 to 9</td>
<td>1</td>
</tr>
<tr>
<td>Doses post-remission (varies by ALL risk group)*</td>
<td>6 to 36</td>
<td>1</td>
</tr>
<tr>
<td>Vials to complete all treatment**</td>
<td>12 to 42</td>
<td>2 to 7</td>
</tr>
</tbody>
</table>

* Some protocols in high-income countries use many more doses of asparaginase in higher-risk patients, but in general post-remission ratios of native E coli asparaginase to PEG-E coli asparaginase are 6 to 1.

** Assuming no obesity and only 6 doses of native E coli during induction.

### Vials per treatment course with native E coli versus PEG-E coli asparaginase

On average the ratio of E coli asparaginase needed versus vials of PEG-E coli asparaginase is 10.3 assuming no obesity and no ability to share vials of PEG-E coli asparaginase by splitting a vial between two patients (a common practice in LMIC). This means that a per-vial price of PEG-E coli asparaginase that is 10.3 times greater than that of a vial of native E coli asparaginase would be cost-neutral, without considering the differences in efficacy. High quality brands of native E coli asparaginase from reputable companies typically cost $150 to $177 per vial and Oncaspar (the originator PEG-E coli asparaginase marketed by Servier) costs $1300 to $1400 per vial in much of Europe and Latin America. Because of the greatly reduced rates of hypersensitivity and neutralizing antibodies (and thus the decreased relapse risk) with the PEGylated product, it would be cost-effective even if it cost 100 times more than native E coli asparaginase rather than 10 times more (as it does in the USA, where the per-vial cost is about $14,000). The mistake that some governments have made is to purchase a low-quality native E coli asparaginase at a very low price (sometimes as low as $20 per vial) in an effort to reduce costs. Asparaginase is a biological therapy whose manufacture is complex, and it must be refrigerated at all times from the factory to the patient, which imposes costs on suppliers and distributors that must be recouped. Any gaps in the cold chain can lead to less active, more impure product with the consequent increase in relapse, which not only reduces the patients chances for survival, but also greatly increases healthcare costs since ALL salvage therapy is very expensive. A sustainable supply of high-quality asparaginase is therefore not only effective but cost-effective, and worth the investment required. A single vial of PEG-E coli asparaginase 3750 U can often be shared between 2 or even 3 patients, which can further reduce costs, and in some LMIC, protocols have been designed that include flexibility in the timing of asparaginase administration to reduce costs (e.g. instead of “Day 4 of induction” the protocol reads “Between day 4 and day 11 of induction” to allow all patients receiving asparaginase therapy to be
scheduled on the same day of the week and thus minimize waste from an unused portion of a vial). Others are studying the safety of using the remaining drug from an open vial on a future date, but this practice may expose patients to risk of infection so cannot be recommended without further safety data.

12. **Summary and Conclusions**

   i. Strength of recommendation: Very strong

   ii. Rationale: Acute lymphoblastic leukemia is curable in more than 80% of cases with the use of high-quality asparaginase as part of a multi-drug regimen (whose other components are already listed in the EML).

   iii. PEGylated *E coli* asparaginase has a lower rate of hypersensitivity and a much lower rate of neutralizing antibody formation than native *E coli* asparaginase, so is critical in countries where no second-line asparaginase (*Erwinia*) is available.

**References**


