(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☒ No ☐

Please provide brief details:

Acute-lymphoblastic (ALL) is the most common childhood cancer accounting for one-quarter of all childhood malignancies. It has a 5-Year event free survival rate between 60-70 % in young patients from low- and middle-income countries. In adolescents and young adults 5-year event free survival is 30-40 %. The improvement in survival is related to aggressive administration of multi-drug regimens during induction and consolidation followed by maintenance. Asparaginase is an integral component of both induction and consolidation in the treatment of ALL.

(2) Have all important studies/evidence of which you are aware been included in the application?

Yes ☒ No ☐

Please provide brief comments on any relevant studies that have not been included:

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☒ No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

2 types of reactions are noted with asparaginase therapy:

1) In up to 70% of patients Asparaginase results in allergic hypersensitivity reactions at some point time during therapy depending on treatment schedule and concomitant therapy. The risk of reaction increases with number of doses and up to one-third of patients experience a hypersensitivity reaction by the fourth dose. This is one of the highest reported hypersensitivity reactions reported from chemotherapy drugs. Approximately 10% are life-threatening.
2) Additionally, in some 5-10% patients there is formation of silent neutralizing antibodies resulting in inactivation of asparaginase and a lower threshold of drug in the blood stream. This results in a low therapeutic threshold of the drug. For these patients, therapeutic drug monitoring is essential, unfortunately this is generally not available in LMICs. Besides it is expensive and requires frequent monitoring.

In these two groups of patients’ alternatives include pegylated asparaginase and Erwinia asparaginase. It is essential for patient to continue therapy with some form of asparaginase to achieve cure.

Pegylated asparaginase results in longer period of asparagine depletion with comparable toxicity. Erwinia asparaginase is more expensive then pegylated asparaginase.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

There are efficacy reports of pegylated asparaginase from Asia, Europe and North America and Asia.

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☒ No ☐

Please provide brief details:
The adverse effects are similar to those with asparaginase treatment.

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Pegylated asparaginase is more expensive but the cost is also offset by decreasing the number injection given.

With pegylated asparaginase the number of allergic reactions is lower.

Less frequent doses are required: 1 dose of pegylated asparaginase is equivalent to 9 doses of native asparaginase.

More compliance and less chemotherapy visits

Less immunogenic with resultant antibody formation

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☐ No ☒

Please provide brief details:
(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☒ No ☐

Please provide brief details:

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☒ No ☐

Please provide brief details:

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

Pegylated asparaginase is more expensive than native asparaginase. However, ALL is potentially curable in 60-70% patients especially in the younger population. In this scenario a relatively more expensive drug to attain cure is acceptable.

(10) Any additional comments?

In countries who cannot afford pegylated asparaginase initially, asparaginase can be given initially and if hypersensitivity reactions develop or with formation of neutralizing antibodies patients can be shifted to the pegylated asparaginase.

(11) Please frame the decisions and recommendations that the Expert Committee could make.

APPROVED

(12) References (if required)