




		EMLc	ATC codes: L01XX24
Indication	Lymphoid leukaemia, not elsewhere classified	ICD11 code: 2C03.3	
INN	Pegaspargase		
Medicine type	Biological agent		
List type	Core		
Additional notes	Including quality-assured biosimilars		
Formulations	Parenteral > General injections > IV: 3750 units per 5 mL in vial		
EML status history	First added in 2019 (TRS 1021)		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	The recommendation is for this specific medicine		
Patent information	Patents have expired in most jurisdictions Read more about patents . 		
Tags	Biosimilar		
Wikipedia	Pegaspargase 		
DrugBank	Pegaspargase 		

Expert Committee recommendation

The Expert Committee recommended the addition of pegaspargase to the complementary list of the EML and EMLc for use in the treatment of acute lymphoblastic leukaemia. The listing should indicate that quality-assured biosimilars of pegaspargase should also be considered as essential. The Committee noted pegaspargase was associated with less immunogenicity and development of neutralizing antibodies than native asparaginase, which may offer advantages in terms of improved patient adherence enabling completion of treatment, thereby reducing the risk of relapse.

Background

The application requested the addition of pegaspargase (PEGylated Escherichia coli asparaginase) to the EML and EMLc for use in the treatment of acute lymphoblastic leukaemia (ALL). Pegaspargase had not previously been considered by the Expert Committee for addition to the EML. Native E. coli asparaginase is currently included on the EML and EMLc for treatment of ALL. 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 three asparaginases effectively treat ALL.

Public health relevance

Acute lymphoblastic leukaemia (ALL) is a rare haematological malignancy. Globally, from 2003 to 2007, the age-standardized incidence rate of ALL ranged from 1.08 to 2.12 per 100 000 person-years. ALL accounts for approximately 25% of all cancers (80% of leukaemias) in children. The disease is far less common in adults (<1% of all cancers) where it is associated with much lower cure

rate that that achievable for children (1). Allergic reactions to native *E. coli* asparaginase occur in 20% to 42% of patients with ALL, and silent (asymptomatic) neutralizing antibody formation in another 30 to 40%, such that around two thirds of patients do not complete all their required asparaginase unless they have access to a second asparaginase product, usually *Erwinia* asparaginase (2–10). Hypersensitivity or silent antibody formation necessitate a change to another form of asparaginase. The supply of *Erwinia* asparaginase has been limited to high-income countries, and supply is often insufficient to meet the needs of patients who react to first-line native *E. coli* asparaginase. 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% (11). Furthermore, relapse therapy entails intense salvage chemotherapy followed by allogeneic stem cell transplantation, which greatly increases treatment costs (9). Minimization of allergic reactions to the initial form of asparaginase improves outcomes and reduces costs.

Benefits

PEGylation of *E. coli* asparaginase to create pegaspargase increases the half-life of asparaginase and decreases immunogenicity and allergic reactions/antibody formation from 20–42% to 2–11% (12). The UKALL 2003 trial used pegaspargase in a schedule that included several days of glucocorticoids prior to each dose of pegaspargase in low- and intermediate-risk patients. Glucocorticoid pre-treated patients had a 1% rate of allergic reaction and five-year event-free survival of around 95% (13). Patients in the high-risk arm received several doses of pegaspargase without preceding glucocorticoids and had a reaction rate of 6%, such that in the whole study the reaction rate was 2% (13, 14). These findings led to a change in clinical practice, and modification of existing ALL treatment protocols to include glucocorticoid pre-treatment before each pegaspargase dose, to reduce the incidence of allergic reactions, thus allowing patients to complete asparaginase therapy and reducing the need for a second-line asparaginase (e.g. *Erwinia*). Asparaginase products have different molecular structures, different half-lives, and different clinical activities per unit. Pegaspargase is six to nine times more potent than native *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 pegaspargase to provide the asparaginase needed for patients. Treatment strategies using pegaspargase 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 more patients to continue first-line asparaginase and complete all doses of the treatment protocol. Completion of all doses of first-line asparaginase reduces the risk of relapse and thus reduces costs associated with salvage therapy (15). It also reduces the need for second-line *Erwinia* asparaginase, which is not available in many countries (especially LMICs) and which has suffered from recurrent shortages and stock-outs even in high-income countries (HICs).

Harms

No data were presented in the application in relation to the comparative safety of pegaspargase.

Additional evidence

A randomized, open-label Phase III trial compared the relative toxicity and efficacy of intravenous (IV) pegaspargase and intramuscular (IM) native *E. coli* asparaginase in 463 children with newly diagnosed ALL who had achieved complete remission following induction therapy (16). Five-year disease-free survival was similar between treatment groups: 90% vs 89% for IV pegaspargase and IM native *E. coli* asparaginase treated patients, respectively ($p=0.58$). There was no significant difference in the frequency of asparaginase-related toxicities (allergy, pancreatitis or thrombotic or bleeding adverse events) between the treatment groups: 28% vs 26% in the pegaspargase and native *E. coli* asparaginase groups, respectively ($p=0.60$). Pegaspargase was associated with less anxiety than native *E. coli* asparaginase. The most common adverse events of Grade 3 or higher were infections (bacterial or fungal) and occurred at a similar rate in both treatment groups. A retrospective study compared the efficacy and safety of pegaspargase and native *E. coli* asparaginase in 122 adolescents and adults with newly diagnosed ALL (17). Both treatments demonstrated comparable complete remission rates (95.65 vs 90.79%), median overall survival (14.07 vs 16.29 months) and median relapse-free survival (10.00 vs 8.57 months). Pegaspargase-treated patients aged less than 35 years had a higher median relapse-free survival time compared with *E. coli* asparaginase-treated patients (10.93 vs 8.97 months; $p=0.037$). Both treatments were found to be acceptably tolerable and demonstrated similar incidences of allergy, hepatic toxicity, pancreatic lesions, and bleeding and coagulation effects. In patients with relapsed ALL, and with hypersensitivity to native *E. coli* asparaginase, pegaspargase treatment was associated with similar tolerability as in newly diagnosed patients (18).

Cost / cost effectiveness

The application estimated that, on average, the ratio of the number of vials of E. coli asparaginase needed versus vials of pegaspargase was 10.3 (assuming no obesity and no vial sharing between patients) meaning that a per-vial price of pegaspargase that is 10.3 times greater than that of a vial of native E. coli asparaginase would be cost-neutral, without considering differences in efficacy. Costs for native E. coli asparaginase were reported as between US\$ 150–177 per vial, compared to US\$ 1300–1400 per vial for pegaspargase in Europe and Latin America.

WHO guidelines

None available.

Availability

Pegaspargase is marketed by Servier Pharmaceuticals. Biosimilars of pegaspargase are in development in some jurisdictions.

Other considerations

The risk of allergic hypersensitivity reactions to asparaginase therapy increases with the number of doses and up to one third of patients experience a reaction by the fourth dose. This is one of the highest reported sensitivity reactions reported from chemotherapy drugs. Approximately 10% of reactions are life-threatening. Reactions involving the formation of silent neutralizing antibodies result in inactivation of asparaginase and reduced serum asparaginase activity levels. This results in a low therapeutic threshold of the drug. For these patients, therapeutic drug monitoring is essential, but not generally available in LMICs.

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