Rituximab

Essential medicine status

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

EMLc | ATC codes: L01FA01

Indication	Diffuse large B-cell lymphoma, not otherwise specified ICD11 code: 2A81.Z
INN	Rituximab
Medicine type	Biological agent
List type	Complementary
Additional notes	Including quality-assured biosimilars
Formulations	**Parenteral > General injections > IV:** 100 mg per 10 mL in 10 mL vial ; 500 mg per 50 mL in 50 mL vial
EML status history	First added in 2015 (TRS 994) Changed in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer Biological
Wikipedia	Rituximab
DrugBank	Rituximab

Expert Committee recommendation

The Expert Committee recommended the addition to the complementary list of the EMLc of ATRA, dasatinib, fluorouracil, imatinib, irinotecan, nilotinib, oxaliplatin, procarbazine and rituximab for the paediatric cancer indications outlined in the table below. The Committee also recommended the extension of the current listings on the EMLc of bleomycin, doxorubicin, vincristine, cisplatin, cyclophosphamide, prednisolone, cytarabine, daunorubicin, mercaptopurine, methotrexate, cytarabine and hydroxycarbamide to include the indications outlined in the table below. The Committee also recommended the addition to the core list of the EMLc of enoxaparin with a square box for use as an anticoagulant in children. The Expert Committee did not recommend the addition of zoledronic acid to the complementary list of the EMLc for the treatment of malignancy-related bone disease. The Committee noted that data for its use in children are scant and fragmented. The Committee was also concerned that the effects of zoledronic acid in some paediatric cancers (e.g. osteosarcoma) were largely negative, and that there are insufficient long-term safety data of bisphosphonate use in paediatric cancer patients to be reassured of an acceptable benefit–to–harm ratio. Furthermore, the Committee noted that although use of bisphosphonates in paediatric patients has been reported to be well tolerated, the impact of use in the context of patients with actively growing skeleton is not yet fully known. New medicines for EMLc All-trans retinoic acid: Acute promyelocytic leukaemia Dasatinib: Imatinib-resistant chronic myeloid leukaemia Fluorouracil: Nasopharyngeal carcinoma, early-stage colon cancer, early-stage rectal cancer, metastatic colorectal cancer Imatinib: Chronic myeloid leukaemia, gastrointestinal stromal tumour Irinotecan: Metastatic colorectal cancer Nilotinib: Imatinib-resistant chronic myeloid leukaemia Oxaliplatin: Early stage colon cancer, metastatic colorectal cancer Procarbazine: Hodgkin lymphoma Rituximab: Diffuse large B-cell lymphoma Enoxaparin: Anticoagulant (core list) Extension of indications for currently listed medicines Bleomycin: Kaposi sarcoma Doxorubicin: Kaposi sarcoma Vincristine: Kaposi sarcoma Cisplatin:

Nasopharyngeal carcinoma Cyclophosphamide: Diffuse large B-cell lymphoma Prednisolone: Diffuse large B-cell lymphoma Cytarabine: Acute promyelocytic leukaemia, acute myelogenous leukaemia Daunorubicin: Acute promyelocytic leukaemia Mercaptopurine: Acute promyelocytic leukaemia Methotrexate: Acute promyelocytic leukaemia Hydroxycarbamide: Chronic myeloid leukaemia To help improve access, the Committee recommended the current listing for intravenous rituximab on the EML should indicate that quality-assured biosimilars of rituximab should also be considered as essential medicines. In addition, the Expert Committee recommended that WHO continue to facilitate access to biosimilars through the Prequalification programme and WHO Collaborative Registration Procedure.

Background

The application proposed an extension of adult cancer indications to paediatrics and corresponding inclusion on the EMLc. The proposal involves both the inclusion of new indications for some cancer medicines currently on the EMLc and the addition of selected new cancer and supportive care medicines to the EMLc. (Refer to TRS 1021 for the proposed listing extensions). The proposed medicines and corresponding indications had not previously been considered for inclusion on the EMLc. The application applied the following rationale in proposing the medicines and indications for inclusion on the EMLc: ■ The medicine must already be listed on the EML or EMLc. ■ The indications listed for adults are also diagnosed in children aged 12 years and under. ■ The medicines have been reported for treatment in children aged 12 years and under for the same indication as listed on the EML for treatment in adults. ■ Published literature supports the extension of the indication to children, including clinical studies, peer-reviewed consensus documents and/or clinical guidelines support the medicine’s role as standard of care.

Public health relevance

Cancer is a leading cause of death for children globally with the most common cancer types occurring in children being leukaemias, lymphomas and central nervous system tumours (1). Childhood cancers generally cannot be prevented nor screened for, so improving outcomes for children with cancer relies on early and accurate diagnosis and access to effective treatments. In 2018, WHO launched the Global Initiative for Childhood Cancer, to provide leadership and technical assistance to Member States to build and sustain high quality childhood cancer programmes. The goal of this initiative is to achieve at least 60% survival for all children with cancer globally by 2030 (2).

Benefits

Acute promyelocytic leukaemia (APML) New medicine: all-trans retinoic acid (ATRA) New indication: cytarabine, daunorubicin, mercaptopurine, methotrexate The median age of children with APML has been reported as 10 years (3). Standard regimens used for children with APML include ATRA (3, 4), with prior randomized trial data demonstrating significant disease-free survival improvement for children randomized to receive ATRA vs not (48% at 5 years, vs 0%, $p<0.0001$), with overall survival rates sustained at 10 years (5). The use of ATRA is acknowledged in standard guidelines for the treatment of APML, and is considered to be a paradigm for a targeted approach to the treatment of leukaemia (6–10). The treatment of APML is typically provided in the context of poly-chemotherapy, involving cytarabine, daunorubicin, mercaptopurine and methotrexate (3–5). Acute myeloid leukaemia (AML) New indication: cytarabine The safety and effectiveness of cytarabine for the treatment of childhood AML have been evaluated in controlled clinical trials (11–13). It is considered the standard of care, used internationally for children with AML, as in adults (14, 15). Chronic myeloid leukaemia (CML) New medicines: imatinib, dasatinib, nilotinib, hydroxycarbamide CML is a very rare disease in children, estimated to be responsible for 2% of all leukaemias in children less than 15 years of age with an annual incidence of one case per million children in that age range (16). The tyrosine kinase inhibitors introduced a chance of cure for CML, with long lasting disease control and significantly improved outcomes (17). Imatinib has shown clinical benefit in children with CML, with results comparable to those seen in adults (18). In particular, a clinical study of the use of imatinib in patients aged less than 18 years with CML in the chronic phase demonstrated the efficacy, safety and long-term benefit of imatinib in children (19). Dasatinib and nilotinib have been used in children with CML including (but not limited to) imatinib-resistant cases. A Phase II trial of dasatinib in 113 paediatric patients with CML demonstrated a complete cytogenetic response was achieved in 76% of imatinib-resistant patients, with an acceptable safety profile that did not include pleural or pericardial effusion, commonly seen in dasatinibtreated adults (20). The effectiveness and safety of nilotinib in children with CML has also been reported (21). Nilotinib has been approved by the United States FDA for treatment of paediatric patients with newly diagnosed or resistant CML on the basis of the results from two open-label, single-arm trials involving 69 patients (22, 23). For imatinib-resistant patients, the major molecular response rate was 40.9%. No new safety concerns were reported, noting transient and manageable laboratory abnormalities: hyperbilirubinaemia and moderate to severe transaminitis. Hydroxycarbamide has a recognized debulking/cytoreductive role for myeloid malignancies and for palliative purpose in all settings. In addition, hydroxycarbamide can have an important role in settings where resource limitations affect access to imatinib or other tyrosine kinase inhibitors, to allow commencement of antineoplastic therapy (24). A general expert consensus

recommendation for childhood CML includes hydroxycarbamide as standard initial therapy in all settings, while awaiting confirmatory diagnostic testing results as well as initial clinical response (25). Gastrointestinal stromal tumour (GIST) New medicine: imatinib Imatinib is the preferred treatment for molecularly-selected GIST in adults and children, where c-KIT sensitive mutations are demonstrated. Paediatric GISTs represent a distinct entity, and may be associated with genetic syndromes (such as Carney Triad, Carney-Stratakis syndrome or neurofibromatosis 1 (NF1)/ Von Recklinghausen disease). It is also less common for paediatric patients with GIST to have the activating mutations in KIT and platelet-derived growth factor receptor alpha (PDGFRA) seen in adults. Data on the effectiveness and activity of imatinib in paediatric GIST is scarce, as it is a very rare entity (1–2% of all the cases). Children less than 18 years of age typically have more indolent disease with more favourable prognosis than in adults (approximating 100% five-year overall survival), as reported in a long-term retrospective analysis of a large observational study, that included a sub-group of 28 patients in this age group (26). Diffuse large B-cell lymphoma (DLBCL) New medicine: rituximab New indication: cyclophosphamide, doxorubicin, prednisolone, vincristine Different studies of DLBCL have established a role for rituximab in paediatric populations, with studies often spanning all age groups including adults and children starting at age 9 years (27), and confirming efficacy and safety in children (28). Rituximab is administrated in the context of a combination regimen with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) (27, 28). CHOP alone may be administered in settings where rituximab is not available. Kaposi sarcoma New indication: bleomycin, doxorubicin, vincristine Kaposi sarcoma in children primarily occurs as either endemic (HIV-unrelated) or epidemic (HIV-related) disease. According to the data known from registries and literature, Kaposi’s sarcoma primarily occurs in the elderly population of the Mediterranean region, while the occurrence in children is restricted to smaller series (29). Data from paediatric cohorts and clinical trials showed a median age of diagnosis at 8 years old. Chemotherapy indicated for Kaposi sarcoma includes bleomycin, vincristine and doxorubicin (30–34). One of the regimens combining doxorubicin, bleomycin and vincristine (ABV) has reported 80% remission for stage I HIV-positive patients treated in South Africa (32). Bleomycin, vincristine and doxorubicin have also been included as standard treatment agents in international expert consensus recommendations (35). Nasopharyngeal cancer New indication: cisplatin, fluorouracil Nasopharyngeal carcinoma (NPC) is the most commonly diagnosed head and neck malignant neoplasm in China and South-East Asian countries, but is considered relatively rare among children. Treatment schemes are typically adapted for children from adult-based regimens. Cisplatin-based regimens are the standard of care for children with NPC. Together with cisplatin, fluorouracil (5-FU) is included in standard regimens for children with NPC, with standard administration of two courses 21 days apart (36–39). The use of cisplatin including as a radiosensitizer (with concomitant cisplatin and radiation therapy) following cisplatin/5-FU in the systemic treatment of NPC in children is recognized as standard across different institutions and countries, extrapolating from the adult treatment experience (40–43). Colon and rectal cancers New medicine: irinotecan, oxaliplatin New indication: cisplatin, fluorouracil While very rare, colorectal cancers can occur in children (reported in as young as nine months old) and typically utilize the same chemotherapy agents as in adults, including 5-FU for the neoadjuvant treatment of rectal cancer, 5-FU and oxaliplatin for the adjuvant treatment of colon and rectal tumours, and 5-FU, oxaliplatin and irinotecan for advanced or metastatic colorectal cancer (44–47). Hodgkin lymphoma New medicine: procarbazine Procarbazine is commonly included as a drug of choice in children for the treatment of Hodgkin lymphoma. According to clinical guidelines and literature, procarbazine is a standard inclusion in multi-agent chemotherapy regimens for Hodgkin lymphoma in children (48, 49). For the paediatric population, multiple regimens containing procarbazine are used, in particular BEACOPP that contains bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. It is often used in more resource-limited settings. Local selection and use should consider known gonadotoxicity and effects on male fertility (50). Malignancy-related bone disease New medicine: zoledronic acid Although certain malignancy-related bone diseases, such as osteonecrosis, occur more often in older children, patients as young as age 4 to 6 years have been affected and required treatment (51–53). The administration of zoledronic acid in paediatric oncology appears safe, and may result in improved bone strength and pain control. In a retrospective chart review of inpatients and outpatients less than 21 years old who received zoledronic acid at the Children's Hospital of Philadelphia, safety of the bisphosphonate was assessed. The safety profile was consistent with the known experience in adults, including preventable alterations in calcium levels, with no major side-effects reported (51). Anti-coagulation New medicines: enoxaparin The use of low molecular weight heparin (LMWH) as an anticoagulant is considered standard of care for prophylaxis and treatment in children, including but not limited to children with cancer. Malignancy as well as treatment-related factors such as immobilization and central venous access can increase risk for thrombosis (54). Enoxaparin as standard antithrombotic therapy is used as a first option in routine practice in many settings (55–57).

Harms

Not reported separately in the application.

Cost / cost effectiveness

Not reported in the application.

Availability

The proposed medicines are already included on the EML and/or EMLc.

Other considerations

The Expert Committee recognized the public health need for access to cancer therapies for children. The Committee acknowledged that there is limited clinical trial evidence available for the use of many cancer medicines in children, and that it is often necessary to rely on extrapolated data from trials in adults, clinical consensus and/or clinical practice guidelines, that lend support to a medicine's role as the standard of care in paediatric patients. Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence & Injury Prevention. The technical unit advised that it supports the proposal to extend the listing of specified cancer medicines and indications on the EML to the EMLc. The Committee noted the correspondence from the European Society for Medical Oncology (ESMO) requesting recognition of biosimilars of rituximab and trastuzumab on the EML. The Committee agreed that quality-assured biosimilars of these monoclonal antibodies represent an opportunity for expanding affordable access to cancer medicines for health systems.

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