Nilotinib

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

### Indication
Chronic myeloid leukaemia, not elsewhere classified

### INN
Nilotinib

### Medicine type
Chemical agent

### List type
Complementary

### Additional notes
Imatinib-resistant chronic myeloid leukaemia

### Formulations
Oral > Solid: 150 mg capsule; 200 mg capsule

### EML status history
First added in 2017 (TRS 1006)
Changed in 2019 (TRS 1021)

### Sex
All

### Age
Also recommended for children

### Therapeutic alternatives
The recommendation is for this specific medicine

### Patent information
Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org. Read more about patents.

### Tags
Cancer

### Wikipedia
Nilotinib

### DrugBank
Nilotinib

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**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 hydroxyurea 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 fragmentated. 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/L: Kaposi
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...
Enoxaparin as standard antithrombotic therapy is used as a first option in routine practice in many settings (55–57). Malignancy as well as treatment-related factors such as immobilization and central venous access can increase risk for thrombosis is considered standard of care for prophylaxis and treatment in children, including but not limited to children with cancer. Reported (51). Consistent with the known experience in adults, including preventable alterations in calcium levels, with no major side-effects zoledronic acid at the Children's Hospital of Philadelphia, safety of the bisphosphonate was assessed. The safety profile was strength and pain control. In a retrospective chart review of inpatients and outpatients less than 21 years old who received treatment (51–53). The administration of zoledronic acid in paediatric oncology appears safe, and may result in improved bone such as osteonecrosis, occur more often in older children, patients as young as age 4 to 6 years have been affected and required fertility (50).

It is often used in more resource-limited settings. Local selection and use should consider known gonadotoxicity and effects on male 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.

Additional evidence

A randomized, multicentre, open-label Phase III trial (OS2006) compared standard chemotherapy with or without zoledronic acid in 318 patients aged between 5 years and 50 years (median 15.5 years) with newly diagnosed highgrade osteosarcoma (58). The trial results indicated that zoledronic acid did not improve event-free survival, percentage of good histological response or overall survival. No significant differences in toxicity or orthopaedic complications were observed between treatment groups. The trial was stopped after the second interim analysis for futility and the authors concluded that the use of zoledronic acid in osteosarcoma patients was not recommended. A retrospective analysis of the use of zoledronic acid for treatment of chemotherapy related osteonecrosis in 20 children and adolescents with osteonecrosis found that zoledronic acid was well tolerated and improved joint pain in the majority of patients (53). However, among patients with osteonecrosis of the hip, the majority had progressive joint destruction requiring arthroplasty, despite treatment with zoledronic acid.

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.