# Doxorubicin

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.1. Cytotoxic medicines

EMLc | ATC codes: L01DB01

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|---|---|
| **Indication** | Rhabdomyosarcoma primary site ICD11 code: 2B55.Z |
| **INN** | Doxorubicin |
| **Medicine type** | Chemical agent |
| **List type** | Complementary |
| **Formulations** | **Parenteral > General injections > IV:** 10 mg in vial (hydrochloride) ; 50 mg in vial (hydrochloride) |
| **EML status history** | Application rejected in 2021 (TRS 1035) |
| **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<br>Read more about patents. |
| **Tags** | Cancer |
| **Wikipedia** | Doxorubicin |
| **DrugBank** | Doxorubicin |

## Expert Committee recommendation

The Expert Committee noted that doxorubicin when added to standard triplet chemotherapy (e.g. IVA and VAC) in patients with rhabdomyosarcoma at high risk of relapse was not associated with increased survival benefit but was associated with increased toxicity. Severe leukopenia, anaemia, gastrointestinal adverse events and infections were more common when doxorubicin was added to combination chemotherapy (e.g. IVA and VAC). The Committee also noted that doxorubicin was also associated with important cardiotoxicity, especially in children. Therefore, cardiac function has to be evaluated at baseline and at intervals during treatment. In addition, the Committee noted that tumour responses associated with doxorubicin used as a single agent were usually short-lived. The Committee considered that the benefit-to-risk ratio of doxorubicin was not favourable in both low- and high-risk patients, and therefore did not recommend the addition of doxorubicin to the complementary list of the EML or EMLc for the new indication of metastatic or non-metastatic rhabdomyosarcoma.

## Background

The application presented a review of evidence for doxorubicin in the treatment of rhabdomyosarcoma. Based on

the findings of the review, doxorubicin was not proposed by the applicants for inclusion on the Model Lists for this indication. Doxorubicin has been included on the EML and EMLc since the first editions of the lists in 1977 and 2007, respectively. The currently endorsed indications for doxorubicin on the Model Lists are: • EML: acute lymphoblastic leukaemia, Burkitt lymphoma, diffuse large B-cell lymphoma, early stage breast cancer, Ewing sarcoma, follicular lymphoma, Hodgkin lymphoma, Kaposi sarcoma, metastatic breast cancer, multiple myeloma, nephroblastoma and osteosarcoma • EMLc: acute lymphoblastic leukaemia, Burkitt lymphoma, diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, Kaposi sarcoma, nephroblastoma and osteosarcoma. Medicines currently included on the EML and EMLc for the treatment of rhabdomyosarcoma are those recommended in the standard ifosfamide, vincristine and dactinomycin (actinomycin-D) (IVA) regimen, and vincristine, dactinomycin and cyclophosphamide (VAC) regimens. Mesna is also included for this indication to accompany the administration of ifosfamide (1).

## Public health relevance

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents, but it is a rare cancer type responsible for around 3% of all paediatric tumours (2). Data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to determine incidence of rhabdomyosarcoma in the United States from 1975 to 2005. Investigators estimated an incidence of 4.4 cases per million children/adolescents a year (3). Rhabdomyosarcoma is divided into six histological groups with different prognoses. Pleomorphic and alveolar rhabdomyosarcoma have the worst overall survival with a 5-year survival of 26.6% and 28.9%, respectively, while embryonal rhabdomyosarcoma has the highest 5-year survival rate (73.9%) (2).

## Benefits

Doxorubicin was considered an effective therapeutic option as a single agent for treatment of rhabdomyosarcoma before the IVA and VAC chemotherapy combinations became the standard of care. With the addition of more medicines, e.g. ifosfamide, in the combinations, the role of doxorubicin and its contribution to overall survival have become less certain (4,5). A multicentre, open-label, phase III randomized controlled trial evaluated the addition of doxorubicin to standard IVA chemotherapy in 484 patients with rhabdomyosarcoma aged between 6 months and 21 years (6). Median follow-up was 63.9 months and during this period neither median overall survival nor median progression-free survival was reached. The 3-year overall survival was 78.3% in the doxorubicin plus IVA group compared with 80.6% in the IVA group (hazard ratio (HR) 1.17, 95% confidence interval (CI) 0.82 to 1.67). The 3-year event-free survival was 67.5% in the doxorubicin plus IVA group compared with 63.3% in the IVA group (HR 0.87, 95% CI 0.65 to 1.16). Overall, the addition of doxorubicin to IVA chemotherapy did not show statistically significant improvements in outcomes, and may decrease overall survival (low-certainty evidence).

## Harms

From the safety analysis of the randomized trial (6), the use of doxorubicin plus IVA was associated with an increased risk of adverse events, including neutropenia (risk ratio (RR) 1.03, 95% CI 0.98 to 1.09) and infections (RR 1.41, 95% CI 1.24 to 1.61). Grade 3 or 4 leukopenia, anaemia, thrombocytopenia and gastrointestinal adverse events were significantly more common in the doxorubicin plus IVA group than the IVA group.

## Additional evidence

A 1977 study evaluated the dose response of doxorubicin in different tumour types. For non-metastatic rhabdomyosarcoma, single-agent doxorubicin produced a tumour response (i.e. reduction in tumour volume) in about 50% of patients. However, the duration of response was limited, with most patients experiencing disease progression after about 3 months (7).

## Cost / cost effectiveness

No economic evaluation studies were identified.

## WHO guidelines

WHO guidelines for the treatment of rhabdomyosarcoma are not available.

## Availability

Doxorubicin has marketing approval from many national regulatory agencies, including the Australian Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and United States Food and Drug Administration. It is currently included on the Model List for other indications and is available in branded and generic forms.

## Other considerations

The EML Cancer Medicines Working Group noted that the addition of doxorubicin to standard chemotherapy for non-metastatic rhabdomyosarcoma was not associated with increased survival benefit and was associated with increased harms. For this reason, it was not proposed for inclusion on the Model Lists by the applicants. However, the Working Group also considered that single-agent doxorubicin is nevertheless an effective treatment option for non-metastatic rhabdomyosarcoma and may have a place in cases where standard chemotherapy regimens are not available. As such, it was considered a valuable treatment alternative. Therefore, the Working Group advised that it supported the inclusion of doxorubicin on the Model Lists for use as a single agent in the treatment of rhabdomyosarcoma when standard chemotherapy regimens (IVA and VAC) are not available and/or affordable. Comments were received from the WHO Department of Noncommunicable Diseases. The technical unit advised that in line with the recommendation from the EML Cancer Medicines Working Group, the inclusion of doxorubicin in the EMLc for rhabdomyosarcoma is justified given that it addresses a cancer type of public health relevance (rhabdomyosarcoma is the most frequent soft tissue sarcoma in children) and has potential benefits as it is more feasible for use where health systems are weak (where standard chemotherapy regimens are not available or accessible).

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994; https://apps.who.int/iris/handle/10665/189763, accessed 16 May 2021).
2. Amer KM, Thomson JE, Congiusta D, Dobitsch A, Chaudhry A, Li M, et al. Epidemiology, Incidence, and survival of rhabdomyosarcoma subtypes: SEER and ICES database analysis. J Orthop Res. 2019;37(10):2226–30.
3. Perez EA, Kassira N, Cheung MC, Koniaris LG, Neville HL, Sola JE. Rhabdomyosarcoma in children: a SEER population based study. J Surg Res. 2011;170(2):e243–51.
4. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008;113(3):573–81.
5. Eriksson M. Histology-driven chemotherapy of soft-tissue sarcoma. Ann Oncol. 2010;21 Suppl 7:vii270–6.
6. Bisogno G, Jenney M, Bergeron C, Gallego Melcón S, Ferrari A, Oberlin O, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet Oncol. 2018;19(8):1061–71.