

# Azacitidine

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](#)

ATC codes: [L01BC07](#)

Indication	Myeloid leukaemia <a href="#">ICD11 code: 2C03.1</a>
INN	Azacitidine
Medicine type	Chemical agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 100 mg in vial powder for injection
EML status history	Application rejected in 2021 ( <a href="#">TRS 1035</a> )
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more <a href="#">about patents</a> . <a href="#">↗</a>

## Tags

Cancer

## Wikipedia

[Azacitidine](#) [↗](#)

## DrugBank

[Azacitidine](#) [↗](#)

## Expert Committee recommendation

The Expert Committee noted that despite the substantial unmet need for effective therapy for acute myeloid leukaemia in patients unsuitable for intensive induction chemotherapy, the clinical impact of injectable azacitidine on survival is small when compared with other medicines listed in the EML, such as cytarabine and daunorubicin. Moreover, treatment with azacitidine is associated with substantial toxicity and increases the need for high-level supportive care, such as red cell and platelet transfusions and antibiotic treatments. Clearer definition of subgroups of patients who benefit the most in terms of increased survival and more compelling evidence of efficacy in the maintenance setting are required before injectable azacitidine could warrant reconsideration. The Committee also noted that, despite the availability of generic formulations, prices are still high and are an important barrier to access in many countries. Therefore, the Committee recommended that azacitidine for acute myeloid leukaemia should not be added to the complementary EML at this time.

## Background

Azacitidine has not previously been considered for inclusion on the EML. Cytarabine and daunorubicin were included on the EML for induction and consolidation therapy of acute myeloid leukaemia following a comprehensive review of cancer medicines undertaken by the Expert Committee in 2015 (1).

## Public health relevance

Acute myeloid leukaemia is a common leukaemia subtype and has a poor prognosis. Globally, almost 120 000 incident cases of

acute myeloid leukaemia were recorded in 2017, with an age-standardized incidence rate of 1.54 per 100 000. Geographically, the highest burden is seen in South Asia and Western Europe regions. Since 1990, the number of deaths related to acute myeloid leukaemia worldwide has almost doubled, from 52 000 to 100 000 in 2017 (2). Most incident cases of acute myeloid leukaemia occur in adults older than 65 years, and this group has a particularly poor prognosis. Patients with acute myeloid leukaemia have a lower baseline quality of life than individuals with other cancers, and the quality of life may be greatly affected because of the treatment (3).

## Benefits

The applicants conducted a literature search for randomized trials and systematic reviews of azacitidine used in treatment of acute myeloid leukaemia and conducted a meta-analysis of the results. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool, and judgements about precision, consistency, directness and likelihood of publication bias were made following the GRADE approach. Four systematic reviews (4–7) (used to identify relevant studies) and nine randomized trials (8–16) were identified. In general, trials included patients older than 65 years and randomized participants to receive azacitidine or a conventional treatment regimen (standard chemotherapy, cytarabine in low dose, lenalidomide or observation only). In most of the identified trials, azacitidine was used during the induction phase. It was used only in the consolidation phase after induction with standard chemotherapy in four trials (9,13,14,16). The meta-analysis undertaken by applicants included six trials (1125 participants) and showed that the use of azacitidine in patients with acute myeloid leukaemia might increase overall survival by about 0.2 months (hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.69 to 1.35). The certainty of the evidence was judged low due to imprecision (because the CI does not exclude potential harm with azacitidine) and inconsistency (because of unexplained heterogeneity introduced by one trial (15)).

## Harms

Compared with standard chemotherapy, azacitidine may not increase the risk of adverse events. From the nine trials (1409 participants) included in the meta-analysis, a similar incidence of adverse events was observed with or without azacitidine (relative risk (RR) 0.99, 95% CI 0.80 to 1.23; low-certainty evidence). The most commonly reported adverse events were febrile neutropenia, thrombocytopenia, infection and gastrointestinal symptoms.

## Cost / cost effectiveness

The applicants identified four cost–utility analyses that evaluated the cost–effectiveness of azacitidine for treatment of acute myeloid leukaemia (17) or myelodysplastic syndromes (18–20). One study was excluded from the evidence synthesis due to serious limitations making the results unreliable (20). A cost–utility analysis was done from a third payer perspective based on the Canadian health system (17). Using a 25-month time horizon, the base-case incremental cost–effectiveness ratio for azacitidine compared with conventional care regimens was 160 438 Canadian dollars (Can\$) per quality-adjusted life year (QALY) gained. The incremental cost–effectiveness ratio was similar using a life-time horizon (Can\$ 160 373 per QALY). Incremental cost–effectiveness ratios in the range of Can\$ 50 000–140 000 per QALY gained have been reported for Canadian reimbursement decisions. The cost–utility analyses conducted for azacitidine in myelodysplastic syndromes reported less favourable incremental cost–effectiveness ratios. However, this indication was not considered by the application. The applicants report that national reimbursement agencies in Australia, Peru and the United Kingdom of Great Britain and Northern Ireland have evaluated the cost–effectiveness of azacitidine and, despite ratios higher than standard reimbursement thresholds, they recommended coverage because of the lack of other effective treatments in individuals unsuitable for intensive chemotherapy.

## WHO guidelines

WHO guidelines for the treatment of acute myeloid leukaemia are not available.

## Availability

Azacitidine 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 the United States Food and Drug Administration. It is available in branded and generic forms.

## Other considerations

The EML Cancer Medicines Working Group advised that it does not support the inclusion of azacitidine injection on the EML for the treatment of acute myeloid leukaemia. The Working Group noted that the observed magnitude of benefit for azacitidine in acute myeloid leukaemia in terms of overall survival is modest, and below the threshold for benefit established for EML consideration. The Working Group recognized that acute myeloid leukaemia is a disease with a poor prognosis and an unmet clinical need for effective treatment exists, particularly for older patients (> 60 years). However, azacitidine is not a curative treatment option and provides only a small benefit. Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that, in line with the recommendation from the EML Cancer Medicines Working Group, there is insufficient evidence to justify the inclusion of azacitidine on the EML at this time.

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 9 June 2021).
2. Yi M, Li A, Zhou L, Chu Q, Song Y, Wu K. The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: estimates based on the global burden of disease study 2017. *J Hematol Oncol.* 2020;13(1):72.
3. Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. *Cancer Treat Rev.* 2018;69:224–32.
4. Shapiro RM, Lazo-Langner A. Systematic review of azacitidine regimens in myelodysplastic syndrome and acute myeloid leukemia. *BMC Hematol.* 2018;18:3.
5. Kunacheewa C, Thongthang P, Ungprasert P, Utchariyaprasit E, Owattanapanich W. A systematic review and meta-analysis of the efficacy and adverse events of azacitidine-plus-lenalidomide treatment for patients with acute myeloid leukemia, myelodysplastic syndromes and chronic myelomonocytic leukemia (1). *Hematology.* 2019;24(1):498–506.
6. Wen B, You W, Yang S, Du X. Indirect comparison of azacitidine and decitabine for the therapy of elderly patients with acute myeloid leukemia: a systematic review and network meta-analysis. *Exp Hematol Oncol.* 2020;9:3.
7. Tikhonova IA, Hoyle MW, Snowsill TM, Cooper C, Varley-Campbell JL, Rudin CE, et al. Azacitidine for treating acute myeloid leukemia with more than 30% bone marrow blasts: an evidence review group perspective of a National Institute for Health and Care Excellence single technology appraisal. *Pharmacoeconomics.* 2017;35(3):363–73.
8. Seymour JF, Döhner H, Minden MD, Stone R, Gambini D, Dougherty D, et al. Incidence rates of treatment-emergent adverse events and related hospitalization are reduced with azacitidine compared with conventional care regimens in older patients with acute myeloid leukemia. *Leuk Lymphoma.* 2017;58(6):1412–23.
9. Müller-Tidow C, Tschanter P, Röllig C, Thiede C, Koschmieder A, Stelljes M, et al. Azacitidine in combination with intensive induction chemotherapy in older patients with acute myeloid leukemia: the AML-AZA trial of the Study Alliance Leukemia. *Leukemia.* 2016;30(3):555–61.
10. Schlenk RF, Weber D, Herr W, Wulf G, Salih HR, Derigs HG, et al. Randomized phase-II trial evaluating induction therapy with idarubicin and etoposide plus sequential or concurrent azacitidine and maintenance therapy with azacitidine. *Leukemia.* 2019;33(8):1923–33.
11. Montesinos P, Vives S, Martínez-Sánchez MP, Bergua J, Algarra L, Pilar H, et al. Preliminary results of the flugaza trial: a phase iii randomized, open label study comparing azacytidine versus fludarabine and cytarabine (FLUGA scheme) in elderly patients with newly diagnosed acute myeloid leukemia. *Blood.* 2016;128(22):4036.
12. Medeiros BC, McCaul K, Kambhampati S, Pollyea DA, Kumar R, Silverman LR, et al. Randomized study of continuous high-dose lenalidomide, sequential azacitidine and lenalidomide, or azacitidine in persons 65 years and over with newly-diagnosed acute myeloid leukemia. *Haematologica.* 2018;103(1):101–6.
13. Huls G, Chitu DA, Havelange V, Jongen-Lavrencic M, van de Loosdrecht AA, Biemond BJ, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. *Blood.* 2019;133(13):1457–64.
14. Hunault-Berger M, Maillard N, Himberlin C, Recher C, Schmidt-Tanguy A, Choufi B, et al. Maintenance therapy with alternating azacitidine and lenalidomide in elderly fit patients with poor prognosis acute myeloid leukemia: a phase II multicentre FILO trial. *Blood Cancer J.* 2017;7(6):e568.
15. Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol.* 2010;28(4):562–9.
16. Oliva EN, Candoni A, Salutati P, Di Raimondo F, Reda G, Capelli D, et al. Azacitidine for post-remission therapy in elderly patients with acute myeloid leukemia : final results of the Qoless AZA-Aml randomized trial. *Blood.* 2019;134(Suppl 1):117.
17. Coyle D, Villeneuve PJA. Economic evaluation of azacitidine in elderly patients with acute myeloid leukemia with high blast counts. *Pharmacoecon Open.* 2020;4(2):297–305.
18. Crespo C, Moreno E, Sierra J, Serip S, Rubio M. Cost-effectiveness analysis of azacitidine in the treatment of high-risk myelodysplastic syndromes in Spain. *Health Econ Rev.* 2013;3(1):28.
19. Levy AR, Zou D, Risebrough N, Buckstein R, Kim T, Brereton N. Cost-effectiveness in Canada of azacitidine for the treatment of higher-risk myelodysplastic syndromes. *Curr Oncol.* 2014;21(1):e29–40.
20. Gidwani R, Khan ZM, Fenaux P, Beach CL, Pashos CL. A cost-effectiveness analysis of using azacitidine vs. decitabine in treating patients with myelodysplastic syndromes. *J Med Econ.* 2012;15(1):145–54.

