Clozapine

Essential medicine status ✓

Section: 24. Medicines for mental and behavioural disorders > 24.1. Medicines for psychotic disorders

ATC codes: N05AH02

Indication	Schizophrenia or other primary psychotic disorders ICD11 code: 6A4Z
INN	Clozapine
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 25 mg ; 50 mg ; 100 mg ; 200 mg
EML status history	First added in 2013 (TRS 985)
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 about patents.
Wikipedia	Clozapine
DrugBank	Clozapine

Summary of evidence and Expert Committee recommendations

An application to include clozapine as a complementary medicine for treatment-resistant schizophrenia in adults was submitted by the Department of Mental Health and Substance Abuse, WHO. Expert reviews were prepared by Dr Kuruvilla Prasad Mathews and Mr Andrew Gray. The 17th EML includes haloperidol and chlorpromazine in Section 24.1 (Medicines used in psychotic disorders). In 2009 the evidence review and the consequent recommendations of the guideline development group for WHO's Mental Health Gap Action Programme Intervention Guide identified some medicines, in addition to psychosocial interventions, for the treatment of psychotic disorders. The recommendations identified first-generation antipsychotics (broadly equivalent to typical antipsychotics) haloperidol or chlorpromazine as a first choice, and second-generation antipsychotics (broadly equivalent to the group of atypical antipsychotics) as their alternatives if availability and cost are not constraints (1). The same recommendations reserved clozapine for individuals with psychosis who do not respond to other antipsychotics provided that laboratory facilities are available for regular monitoring of white blood cells. In the pivotal trial comparing clozapine to chlorpromazine published in 1988, 30% of treatment-resistant patients responded to clozapine as compared with 4% to chlorpromazine (2). Later clinical trials have shown a response rate of 30–50% (3). A 2010 guideline from the United Kingdom's National Institute for Health and Care Excellence suggests that clozapine be offered "to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs …" (4). Randomized clinical trials involving a large number of patients have been done with second-generation antipsychotics and two major long-term studies have been conducted by the United States National Institute of Mental Health (5, 6). These studies have shown a broadly similar response rate but differences in adverse effects (5, 6). Clozapine has been shown to be better than other second-generation antipsychotics in patients with an inadequate response to other antipsychotics (7). However, although uncommon, agranulocytosis associated with clozapine treatment is a potentially fatal adverse event. Thus the use of clozapine is restricted to refractory patients principally because of the risk of agranulocytosis and the associated need for white cell monitoring. The application requested the addition of clozapine for the management of cases refractory to other antipsychotics. The Expert Committee therefore decided to recommend addition of clozapine to the complementary list of the EML. References: 1. WHO Mental Health

Gap Action Programme (mhGAP). Geneva: World Health Organization; 2012 (http://www.who.int/mental_health/mhgap/en/, accessed 27 November 2013). 2. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45(9):789-96. http://dx.doi.org/10.1001/archpsyc.1988.01800330013001 PMID:3046553 3. McIlwain ME, Harrison J, Wheeler AJ, Russell BR. Pharmacotherapy for treatment-resistant schizophrenia. Neuropsychiatr Dis Treat. 2011;7:135-49. PMID:21552316 4. The NICE Guideline on core interventions in the treatment and management of schizophrenia in adults in primary and secondary care-updated edition. London: The British Psychological Society and The Royal College of Psychiatrists; 2010 (http://guidance.nice.org.uk/CG82/Guidance/pdf/ English., accessed 27 November 2013). 5. Lieberman JA, Stroup TS. The NIMH-CATIE Schizophrenia Study: what did we learn? Am J Psychiatry. 2011;168(8):770-5. http://dx.doi.org/10.1176/appi.ajp.2011.11010039 PMID:21813492 6. Naber D, Lambert M. The CATIE and CUtLASS studies in schizophrenia: results and implications for clinicians. CNS Drugs. 2009;23(8):649-59. http://dx.doi.org/10.2165/00023210-200923080-00002 PMID:19594194 7. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al.; CATIE Investigators. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163(4):600-10. http://dx.doi.org/10.1176/appi.ajp.163.4.600 PMID:16585434