### 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