A.35	Quetiapine – bipolar disorder – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Bipolar disorders account for about 4% of the global prevalence of mental disorders in 2019, occurring in 40 million people and approximately 1 in 150 adults globally. Quetiapine proved to be one of the treatments supported by the strongest and highest-quality evidence for both the acute treatment and long-term prevention of both acute depression and mania/hypomania Currently, the EML includes only carbamazepine, lithium carbonate, and valproic acid for the treatment of bipolar disorders. Including quetiapine with a "selected" square box symbol (□) including a selection of second-generation antipsychotics (SGAs) (namely, aripiprazole, olanzapine, aliperidone) as therapeutic alternatives to the core list of the EML
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Bipolar disorders account for about 4% of the global prevalence of mental disorders in 2019, occurring in 40 million people and approximately 1 in 150 adults globally. Compared to other mental disorders, bipolar disorder and schizophrenia prevalence varied to a lesser extent across regions, and was similar between males and females. According to meta-analytic studies, the lifetime prevalence of bipolar disorder in the general population has been estimated to be around 1% for bipolar disorder type I and around 1.6% for bipolar disorder type II, with relatively similar prevalence across different countries. In terms of disease burden, the global Disability-Adjusted Life Years (DALYs) for bipolar disorder in 2017 totalled 9.29 million (95% UI 5.87-13.75 million), with an increasing trend over the years (54.4% more from 1990). Overall, the burden of bipolar disorder seems to be similar across sexes. Life expectancy of people with bipolar disorder is lower compared to the general population. A recent meta-analysis of 11 observational studies, including 96 601 individuals, showed a pooled life expectancy of 66.88 years (95% CI 64.47-69.28), which was slightly higher in women compared to men. Weighted average of Years of Potential Life Lost (YPLLs) was 12.89 years (95% CI 12.72-13.07), and was greatest in Africa. Suicide is the most common cause of unnatural deaths in bipolar disorder, with a 20- to 30-fold greater risk compared to the general population. Excess mortality by natural causes could be attributable to multiple factors, such as unhealthy lifestyle (including sedentary habits, smoking, use of alcohol and substances), antipsychotic-induced metabolic side-effects, as well as inequitable medical care. Furthermore, bipolar disorder is associated with a high prevalence of comorbid incident mental health conditions over its course.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The application team provided an extensive and comprehensive review of the body of evidence supporting effectiveness of quetiapine. Additional search did not find any better evidence. Available reviews from Cochrane were old and less comprehensive. The proposed group of anti-psychotics were selected based on superiority to placebo for treatment of both acute and long-term prevention of mania/hypomania and/or depression; moderate to high certainty of evidence; and acceptability superiority or non-inferiority to placebo. 6 systematic reviews informed the choices of these anti psychotics including 4 network meta analysis of RCTs and 2 pairwise meta analysis of RCTs. These results are clearly and transparently provided by the team in the application. Anti psychotics meeting above criteria included aripiprazole, asenapine, olanzapine, paliperidone, and quetiapine. Quetiapine proved to be one of the treatments supported by the strongest and highest-quality evidence for both the acute treatment and long-term prevention of both acute depression and mania/hypomania.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The application provides comprehensive evidence on safety/harms demonstrating superiority of the chosen anti-psychotic following pre defined criteria.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: because leukopenia is a common adverse effect with quetiapine, it will be important to monitor this in clients on this medication.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: Most studies on bipolar disorder compared SGAs or combinations of SGAs and mood stabilizer between each other, while less evidence is available on the comparison between SGAs and mood stabilizers as monotherapies. A Dutch pharmacoeconomic study investigated the cost-effectiveness of mood stabilizers alone (lithium or valproate) compared to lithium plus a second-generation antipsychotic (quetiapine, olanzapine, or risperidone) for the treatment of acute mania. The model estimated treatment direct costs (including hospitalizations, outpatient visits and medications used to treat adverse effects) over a 100-day period of time. Monotherapies with lithium or valproate proved more costly than combination therapies. Among the latter, lithium plus quetiapine was significantly more expensive (2555€) than lithium plus risperidone (2365€) or olanzapine (2429€), due to higher acquisition costs, but it was also associated with less side effects. Different pharmacoeconomic analysis provided evidence of the cost-effectiveness of quetiapine plus lithium combination therapy over lithium alone for the maintenance treatment of bipolar disorder
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: the application assessed regulations and availability of products and excluded already one product that posed a risk of regulatory issues (asenapine)
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: WHO Mental Health Gap Action Programme (mhGAP), Version 2.0 (2016)