A.6_Brexpiprazole – EML

Reviewer summary	☐ Supportive of the proposal ☒ Not supportive of the proposal Justification (based on considerations of the dimensions described below): This application refers to the addition of brexpiprazole tablets (0.25 mg/0.5 mg/1 mg/2 mg/3 mg/4 mg) as an adjunctive treatment to antidepressants for the treatment of adults with major depressive disorders (MDD). Brexpiprazole, as well as other adjunct treatments, is not included in the EML and in the WHO mental health guidelines. MDD is a chronic condition, with significant negative impacts on activities of daily living, quality of life (QoL), cognitive function, and employment status and work productivity. An estimated 3.8% of the population experience depression, including 5% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years. Ref: https://www.who.int/news-room/fact-sheets/detail/depression The goals of treatment in MDD include recovery from symptoms, prevention of relapse with possible impact on social functioning (e.g., holding a job, retaining relationships). Although pharmacological treatments for depressive disorders have continued to evolve over the past few decades, people with MDD may at times require adjunctive treatment to augment their depression therapy. The Application states that approximately 50% of people with MDD experience inadequate responses to antidepressants. Several approaches to adjunctive treatment are available; the use of antipsychotic is one of them. Four recent systematic reviews, one with network meta-analysis, assessed the efficacy and safety of antipsychotics in adjunctive treatment of MDD. Overall, they showed that when added to antidepressants, second-generation antipsychotics, including brexpiprazole, had a modest effect on depressive symptom scores compared to placebo. No clear differences among antipsychotics emerged. There is no evidence of better efficacy and safety compared to other adjunct therapies. Brexpiprazole has a favourable tolerability and safety profile, similar to that of other antipsychotics. While adjunctive therapies with antipsychotics can be cost-effective due to a lower risk of hospitalisation, brexpiprazole prices are, in general, higher than other older antipsychotics or other medicine that can be used as adjunctive therapies. Based on these considerations, this Reviewer does not support the inclusion of brexpiprazole as an adjunctive treatment to antidepressants for the treatment of adult people with MDD at this time. Considering the high burden of MDD especially in people who do not respond to antidepressants, the Expert Committee may encourage the future submission of a comprehensive Application on adjunctive therapy for MDD, to prioritize the best options considering both clinical and budgetary implications.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? The WHO EML lists several medicines for depression, such as amitriptyline and fluoxetine. No adjunctive therapies to antidepressants are included in the WHO EML for adult treatment of MDD. (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☐ Not applicable

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Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? Antipsychotics had significant, thought modest, efficacy on depressive symptom scores compared to placebo (SMD = −0.40; 95% CI, −0.68 to −0.12 for quetiapine; −0.35, −0.59 to −0.11 for olanzapine; −0.28, −0.47 to −0.09 for aripiprazole and −0.25, −0.42 to −0.07 for brexpiprazole). No clear added benefit of brexpiprazole emerged. The certainty of most evidence was low or very low. Ref: http://dx.doi.org/10.1097/MD.0000000000034670	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? Safety profile of brexpiprazole is similar to that of other antipsychotics, including risks of neuroleptic malignant syndrome, tardive dyskinesia, hyperglycaemia/diabetes mellitus/dyslipidaemia, weight gain, pathological gambling and other compulsive behaviours, orthostatic hypotension and syncope during initial dose titration and when increasing the dose.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☐ Yes ☒ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? None	☐ Yes ☒ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? The cost-effectiveness analyses presented in the Application suggest adjunctive therapies with antipsychotics can be cost-effective despite high pharmacy costs because of lower all-cause costs and a greater reduction in hospitalisation. Brexpiprazole prices are variable but in general higher than other older antipsychotics or other medicine that can be used as adjunctive therapies Brexpiprazole patent will expire not before 2033, therefore no generic formulations are available yet	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries?	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? Across all approved indications, brexpiprazole is approved in over 60 countries globally. FDA, but not the European Medicines Agency, approved brexpiprazole as an adjunctive therapy to antidepressants for the treatment of MDD in adults. Brexpiprazole is also approved for this indication in several other countries, such as Canada, Mexico, Indonesia, Japan, Thailand, Argentina, Brazil, Chile, Ecuador, Peru	☐ Yes, for the proposed indication ☒ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable