Comments from the Department of Mental Health, Brain Health and Substance Use

"A.6 – Brexpiprazole for major depressive disorder, as adjunctive treatment to antidepressants" for updating the 2023 Model List of Essential Medicines (EML).

Application number	A.6 – Brexpiprazole for major depressive disorder, as adjunctive treatment to antidepressants
Name of the application	PROPOSAL FOR THE ADDITION OF BREXPIPRAZOLE TABLETS FOR THE ADJUNCTIVE TREATMENT OF ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD) TO THE WORLD HEALTH ORGANIZATION (WHO) MODEL LIST OF ESSENTIAL MEDICINES (EML)
Submitted by	Otsuka Pharmaceutical Inc
Date of submission	October 30, 2024

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LIST OF ABBREVIATIONS

AD = Antidepressant

AP = Antipsychotic

EML = Model List of Essential Medicines

LMICs = Low- and middle-income countries

mhGAP = Mental Health Gap Action Programme

MMD = Major depressive disorder

NNT = Number needed to treat

RCT = Randomised controlled trial

TEAE = Treatment-emergent adverse event

TRD = Treatment-resistant depression

WHO = World Health Organization

Comment on the application

Major depressive disorder (MDD) is a common mental disorder that affects over 280 million people in the world, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years.[1] Depression is the third cause of disability in the global burden of disease accounting for 4.3% of the global burden of disease.[1] The estimates for low- and middle-income countries (LMICs) are 3.2% and 5.1%, respectively. Current predictions indicate that by 2030 depression will be the leading cause of disease burden globally.

Two out of three people suffering from depression do not receive adequate treatment in LMICs.[2,3] In addition to psychosocial interventions, medicines play an important role in the treatment of depression. According to international guidelines, including the Mental Health Gap Action Programme (mhGAP), first-line treatments for depression are psychological and pharmacological interventions, namely antidepressants (ADs). In moderate to severe cases of depression, ADs are recommended as first-line treatment. However, the response to ADs varies across people with depression.[4] It has been estimated that between one-half and two-thirds of people with depression do not reach a response threshold to pharmacological treatments.[5,6] Such non-response to treatment may vary from partial response to complete 'resistance' to treatment.[5,7] The term treatment-resistant depression (TRD) has been used in clinical and research settings over the years, and it generally refers to a depressive episode that failed to respond or remit to at least two pharmacological treatments.[8]

For TRD, different options are recommended by international guidelines. The American Psychiatric Association, the British Association for Psychopharmacology, Canadian Network for Mood and Anxiety Treatments guidelines, NICE, World Federation of Societies of Biological Psychiatry guidelines, American College of Physicians, and the Royal Australian and New Zealand College of Psychiatrists all recommend adjunct second-generation antipsychotics (APs) for patients with depression that do not no respond to or a limited response to ADs.[5,9-14]

A proposal for the inclusion of brexpiprazole as an adjunct treatment for TRD has been submitted to the WHO by Otsuka Pharmaceutical Inc. for consideration for the forthcoming update of the WHO model list of essential medicines (EML).

Brexpiprazole is a second-generation AP and dopamine, serotonin, and noradrenaline activity modulator, which is a partial agonist at serotonin 5HT1A and dopamine D2 receptors and an antagonist at serotonin 5-HT2A and noradrenaline α1B/2C receptors, all at similar potency.[15,16] The proposal provides an overview of the evidence on benefits and harms of brexpiprazole for TRD.

Three placebo-controlled trials were conducted in patients with inadequate response to ADs, and a randomised, active-referenced (adjunctive quetiapine extended release) placebo-controlled study was conducted in patients with MDD. The three placebo-controlled trials (“Pyxis”, “Polaris”, and “Sirius”) showed statistical but uncertain clinical superiority over placebo.[17-19] The difference in depression scores on the MADRS favored brexpiprazole by a mean of 3.21,[17] 1.96,[18] and 2.30[19] points, respectively, at the study endpoint. The active-referenced (adjunctive quetiapine extended release), placebo-controlled study yielded similar results, with

within-group changes from baseline on the MADRS favoring brexpiprazole by 1.4 and 1.1 points versus placebo and quetiapine, respectively. A clinically meaningful within-group change from baseline on the MADRS has been reported to range between a 6- to 9-point reduction in total score.[20]

During the long-term adjunctive brexpiprazole treatment (in a 52-week study from three RCTs with 2944 patients), the most common treatment-emergent adverse events (TEAEs) with an incidence of 5% or greater included weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%), insomnia (6.3%), fatigue (6.1%), viral upper respiratory tract infection (5.4%), and anxiety (5.2%). Most TEAEs were mild or moderate in severity, with severe TEAEs occurring in 7.3% of patients.[21]

In the 52-week, open-label extension, 14.1% of patients discontinued because of TEAEs. The most frequently reported TEAEs were akathisia (10.0%) and weight gain (25.5%). Rates of sedation and somnolence were low (sedation: 3.7%; somnolence: 9.4%). In the study, brexpiprazole was associated with small changes in metabolic parameters and moderate weight increase.[22]

MDD has a complex treatment pattern and a high clinical and economic burden. Although additional treatment options must be available for patients who do not respond to ADs, adjunctive treatments are not currently included in the EML as a category per se. This may be because the EML is not a clinical guideline to advise clinicians in their clinical practice but a model list to guide national drug procurement.

Although brexpiprazole is a second-generation AP mentioned in at least two of the above guidelines,[10,14] it is not unanimously identified as the best adjunctive agent for TRD. Network meta-analyses do not show superiority of brexpiprazole over the second-generation APs already on the EML (risperidone, aripiprazole, quetiapine).[23-26] Furthermore, the latter are more widely available than brexpiprazole and are already off-patent. Finally, there is consolidated evidence that lithium (also already on the EML) offers a robust alternative to all of the above as an adjunct treatment to ADs in the case of TRD, boasting a number needed to treat (NNT) of 5 (against 16 of brexpiprazole).[25]

Brexpiprazole is currently available for use in 59 countries and territories out of 189 listed by the World Bank (31%), and only approximately one-third of these countries/territories are LMICs. Considering that the latest report from the World Bank identifies 136 countries as having low- or middle-income economies, brexpiprazole is currently unavailable in 87% of LMICs.

While brexpiprazole is available in the US for the treatment of schizophrenia and adjunctive treatment of MDD, In the EU, brexpiprazole is available for the treatment of schizophrenia only and not for the adjunctive treatment of MDD.

The US patent information listed in the FDA Orange Book for Brexpiprazole “REXULTI” shows a last patent expiration of April 12, 2033 (US10307419).

Brexpiprazole is not currently recommended for use in any of the WHO guidelines.

In synthesis:

Efficacy over placebo	Not clinically meaningful
Superiority over other second-generation APs already on the list	No
Side effects	Certain. In line with those of a second-generation AP
Cost-effectiveness	Uncertain
Patent	Expires on April 12, 2033
Availability in LMICs	Very low
WHO guidelines	Adjunct treatments are not currently listed on the EML or included in the mhGAP guidelines. Brexpiprazole is not recommended in any WHO guideline

Recommendation for EML committee:

Based on the above review, brexpiprazole has minimal clinical efficacy as an adjunctive treatment option for treatment resistant depression and does not show evidence for additional effectiveness over other second-generation antipsychotics that are currently part of the EML. In view of the side effect profile (especially akathisia), low availability in LMICs and cost profile with an extended patent period, it is difficult to justify the inclusion of brexpiprazole in the list of EML at this point of time.

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