

C.7	Diazepam – addition of note regarding indications and specification of square box alternatives – EML
Draft recommendation	<p><input checked="" type="checkbox"/> Recommended</p> <p><input type="checkbox"/> Not recommended</p> <p>Justification:</p> <p>The reviewer recommends the proposal to add an asterisk to diazepam with the following statement: * “For the short-term emergency management of acute and severe anxiety symptoms only” and to add Lorazepam as therapeutic alternatives (restricted square box (.))</p>
Does the proposed medicine address a relevant public health need?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Treatment of anxiety disorders is a public health need due to their high incidence, early age of onset, tendency to relapse for a long time and for their disabling nature. Anxiety disorders are major drivers of the global burden of disease, as measured in prevalence, disability-adjusted life-years, and years lived with disability.</p> <p>According to the last World Mental Health report, in the last 20 years both depressive and anxiety disorders have consistently been among the top ten leading causes of all years lived with disability (YLD) worldwide. Anxiety disorders alone, are responsible for over 28.6 million YLD, accounting for 3.34% of the total YLD globally. Anxiety disorders are also responsible for over 26.7 million disability-adjusted life years (DALYs) annually, accounting for 1.13% of total estimated DALYs due to any disease.</p> <p>Although guidelines clearly indicate selective serotonin reuptake inhibitors (SSRIs) as the first-choice pharmacological treatment for anxiety disorders, for decades, Diazepam and other Benzodiazepines (BDZs) have been recommended as the standard treatment of anxiety, as they are rapidly effective.</p> <p>Nonetheless, the use of benzodiazepines exposes to risks of: abuse, overdose, misuse; tolerance and physical dependence if prolonged treatment; withdrawal syndrome or rebound effect if prolonged treatment is discontinued abruptly; persistent side-effects in older patients (confusion, unsteadiness).</p>

<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>BDZs may be useful for patients with very distressing or impairing anxiety symptoms in whom rapid symptom control is critical.</p> <p>Two meta-analyses compared the effectiveness of psychological and pharmacological treatments, and the effect of antidepressants and BDZs compared with placebo. Both reviews showed superiority of BDZs to placebo in the treatment of panic disorder in adults (comparative efficacy between different BDZs was not investigated at the trial level). Such results were confirmed by a recent and methodologically sound Cochrane review, which estimated a risk ratio (RR) for response to treatment to be 1.65 [95% confidence interval (CI) 1.39 to 1.96; number needed to treat (NNT) 4] in favor of BDZs. Similar results were also found for generalized anxiety disorder, social anxiety disorder and specific phobias</p>
<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>All BDZs carry an intrinsic potential for abuse, misuse, tolerance and physical dependence, there are some that have been clearly identified by authorities as carrying specific risks for addictive behaviors, for e.g., alprazolam, flunitrazepam, temazepam.</p> <p>Some of the side effects for BDZs are described below:</p> <p>Short-term side effects: drowsiness, confusion, dizziness, feeling sleepy, tired or weak, muscle weakness, memory impairment, impaired coordination, psychomotor retardation, increased anxiety or disinhibition (paradoxical reaction, especially in elderly patients), delirium (especially in elderly patients)</p> <p>Long term side effects: cognitive impairment, increasing the risk of falls and vehicle accidents, depression and emotional blunting (in extreme cases emergence of suicidal ideation)</p> <p>Overdose: extreme sedation or drowsiness, low breathing rate, confusion and difficulty thinking, slurred speech, loss of muscle control, coma and it can be fatal if taken with alcohol or opioids</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>As with all BDZs, they carry potential risks for abuse, misuse, development of tolerance and physical dependence and overdose.</p>

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<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: The use of this product doesn't require special requirements for diagnostics and/or monitoring tests however, clinicians should ensure proper follow up of patients don't develop tolerance or abuse/misuse.</p>
<p>Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: The availability and affordability of BDZs varies widely across countries and according to sector (public versus private), as well as supplier (originator versus generic) prices. Diazepam and Lorazepam are both affordable, broadly available as generic and can be prescribed by non-specialist.</p> <p>Evidence suggests BDZs may be associated with unnecessary costs from medicine ingredient costs, dispensing costs and consultation costs due to misuse and unnecessary prescribing. In a study of the United Kingdom National Health System, 67–72% of total costs related to BZDs were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £115,588,439 to £129,870,520 and a mean yearly unnecessary cost of £38,529,480 to £43,290,173.82 In adults with generalized anxiety disorder, evidence also suggests long-term BZD use increases health care costs significantly. In a retrospective cohort study of 866 adults in the United States also indicated that mean total healthcare costs increased by \$2334 following the initiation of a long-term (>90 days) course of treatment with a BZD treatment (from \$4637 [SD=\$9840] pre-treatment to \$6971 [\$17,002] posttreatment; p<0.01). Costs related to use of BDZs increased by an average of \$1099, due to accident-related encounters (e.g., for treatment of fractures) and care received for other reasons possibly related to BDZ use (e.g., sedation, dizziness)</p>
<p>Are there any issues regarding the registration of the medicine by national regulatory authorities?</p> <p>(e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments: Diazepam was the second BDZ (Diazepam) ever to be released in 1963 by Hoffman la Roche Lorazepam (Ativan, Tavor) was approved by FDA on September 30, 1977 for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. Diazepam and lorazepam are currently off-patent and generic formulations are available globally.</p> <p>Furthermore, Diazepam and lorazepam are the two BDZs with the widest range of clinical indications, being approved to treat generalized anxiety disorder, insomnia, seizures, social phobia, and panic disorder, but are also indicated for premedication before some medical procedures.</p>

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<p>Is the proposed medicine recommended for use in a current WHO guideline?</p> <p>(refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Diazepam is recommended in the WHO Mental Health Gap Action Program (mhGAP) guideline update (2015) for the treatment of epilepsy.</p> <p>However, the Guideline Development Group of mhGAP revision is considering recommending that:</p> <p>“Benzodiazepines should not be used for the treatment of adults with generalized anxiety and/or panic disorder. For emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered but only as a short-term (3-7 days maximum) measure.</p> <p>It is expected that these recommendations will have been approved by the WHO Guidelines Review Committee by the time of the next meeting of the Expert Committee on EML.</p>
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