A.32	Phenelzine – treatment-resistant depression – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: Phenelzine (PLZ) is an antidepressant (AD) of the classic monoamine oxidase inhibitor (MAOI) class. There is a broad consensus among psychopharmacologists that the classic MAOIs—which include PLZ, tranylcypromine (TCP), and isocarboxazid (ISO)—are effective in treating severe depressions and TRD. Clinically, the effectiveness of PLZ may be superior to SSRI, and similar with TCA. PLZ and other MAOIs are typically considered late-line (or last-line) pharmacological treatment agents in TRD. However, due to following reasons, MAOIs are limited used as compared to the newer antidepressants. 1. Contraindications: such as uncontrolled hypertension or hypotension, diabetes, pregnancy, breastfeeding, bipolar disorder etc. 2. Adverse effects: such as in CNS (such as dizziness, headache drowsiness, tremor, twitching etc.), GI (such as dry month, anorexia, NV etc.), hepatic effects, hypotension etc. 3. Drug-drug interaction: such as co-use with other antidepressant agents, some analgesics, anxiety drugs etc. And wash-out period required prior to starting MAOIs. In addition, phenelzine is an inhibitor of CYP3A4, CYP2C19, CYP1A2, CYP2C9, CYP2D6 and CYP2B6; clinically significant interactions may potentially occur at typical therapeutic doses, some studies exist suggesting the need for dose reductions of some medications, such as carbamazepine. The drug interactions are one of major reasons that psychiatrists are reluctant to use MAOIs. 4. Time consuming on titration for start and end use: a longer titration time may be dangerous, and urgent management is especially needed for patients with severe suicidal idea or attempts. And a prompt end use can cause withdrawal symptoms. 5. Dietary requirement, such as high intake of dietary tyramine is liable to cause a significant hypertensive reaction with MAOIs. Phenelzine is not in WHO mhGAP for depressive disorder treatment. More importantly, this medicine is not irreplaceable in the treatment of TRD in clinical practice. Considering the reasons above, the reviewer does not recommend the inclusion of phenelzine (PLZ) as an individual medicine in the Complementary List of Essential Medicines (EMLco) for use in TRD.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The prevalence rates of non-response and incomplete response to an initial AD trial are estimated at 30-50% and 60-70% respectively in major depressive disorder (MDD) patients. The personal, societal, and economical burden of TRD is tremendously high. The quality of life in TRD patients is significantly diminished, with substantial reductions in work productivity and general activity levels. There is a high risk of psychiatric and somatic comorbidities, including anxiety disorders, substance abuse, hypertensive diseases etc. TRD incurs an increased suicide risk, 'greater direct and indirect healthcare resource utilization, and greater costs. The TRD treatment on is one of major challenge for clinicians. Although MAOIs is one of choice for TRD, but is not irreplaceable. Personally, MECT or ECT may be safer with rapid response. A meta-analytic review showed that a significant superiority of ECT in all comparisons: ECT versus simulated ECT, ECT versus placebo, ECT versus antidepressants in general, ECT versus TCAs and ECT versus MAOIs. The nonrandomized controlled trials also revealed a significant statistical difference in favour of ECT when confronted with antidepressants drugs. Data analysed suggest that ECT is a valid therapeutic tool for treatment of depression, including severe and resistant forms. (Efficacy of ECT in Depression: A Meta-Analytic Review : The Journal of ECT (lww.com))

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 applicants performed a systematic search for 'phenelzine' on the Cochrane Library archive website on September 12th, 2022. This search returned 236 publications, consisting of 2 Cochrane Reviews and 234 Trials. The selected publications were then reviewed in-depth, but all were either included in the meta-analyses discussed or were of insufficient quality to warrant inclusion; therefore: no additional RCTs or reviews were found. This process was then repeated on PubMed, but no additional publications were found. Meta analyses revealed generally comparable overall efficacy for phenelzine. Drug-placebo differences were 29.5% (+/- 11.1%) (phenelzine; nine studies). For inpatients, phenelzine was 22.3% (+/- 30.7%) (five studies) more effective than placebo. Both phenelzine and isocarboxazid were significantly less effective than comparator tricyclics for inpatients. Both phenelzine and tranylcypromine appear to be more effective than tricyclics in depressed outpatients with atypical features. The applicants also examined the influence of the number of prior treatment trials on TCA versus MAOI on effectiveness in TRD. Results suggest that MAOIs may be more effective than TCAs for early stage TRD. This difference in effectiveness between MAOIs and TCAs diminished as the number of prior treatment trials increased. However, the TCA sample size was limited, and the analysis was retrospective with non-randomized conditions. For the effect size, the results were not consistent: with an effect size of 0.45 (95% confidence interval) for a comparison of MAOIs vs. placebo with an effect size of 0.02 (95% confidence interval: - 0.10-0.14) for a comparison of MAOIs vs. selective serotonin reuptake inhibitors. Other study showed that the effect size for MAOIs vs. tricyclic antidepressants was 0.27 (95% confidence interval: 0.16-0.42).

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: Phenelzine comes with a risk of mild to severe side effects. Most common side effects are mild and can be relieved by adjusting the drug dosage, but some may fatal. These include: Headache, Blurred vision, Dry mouth, Urinary retention and constipation, Sleepiness, Weight gain, Sexual dysfunction, Hypotension. More severe adverse effects of phenelzine use include: seizures, skin rash, liver dysfunction, high sodium levels, suicidal thinking. Additionally, there are two extremely severe side effects of which to be aware: hypertensive crisis and serotonin syndrome. A hypertensive crisis occurs with sudden and severe blood pressure increases, including heart palpitations, light sensitivity, nausea and vomiting, sweating etc Serotonin syndrome is a potentially life-threatening condition that results from elevated levels of serotonin in the brain. Symptoms of serotonin syndrome range from mild to severe, including confusion, diarrhoea, shivering, fever, severe muscle tightness, seizures, even death.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: The potential adverse effects of monoamine oxidase (MAO) inhibitors are more varied and potentially more serious than those reported for most other classes of antidepressant agents. Seriou's reactions requiring discontinuance of therapy can occur and usually involve the cardiovascular, CNS, and hepatic systems. Some of the most serious adverse effects reported with MAO inhibitors (e.g., hypertensive crisis, serotonin syndrome) have occurred when MAO inhibitors were administered concomitantly with certain foods or prescription or nonprescription (OTC) drugs.
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: MAO inhibitors can cause potentially serious adverse effects and should only be used in carefully selected patients who can be closely supervised and only by clinicians who are completely familiar with the proper use, potential adverse effects, and associated precautions and contraindications of the drugs. MAO inhibitors generally are not used as initial therapy in the management of depression but are reserved for patients who do not respond adequately to other antidepressant agents (e.g., selective serotonin-reuptake inhibitors [SSRIs], tricyclic antidepressants) or in whom other therapies are contraindicated.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable Comments: Comparative cost-effectiveness analyses which include MAOI ADs like PLZ and newer ADs are scant. Applicants had an overview of recent prices of PLZ in various countries: (A) A search on pharmachecker.com on 30 October 2022 yielded the following price for PLZ ('Nardil') from Canada (produced by ERFA): $144.95 for 180 tablets. (B) In Belgium, up until the cessation of commercialization in 2019 by Pfizer, the market authorization holder of Nardelzine (PLZ), 3 the price was as follows: tablets 100 x 15 mg R/ €33,48. At present (and since September 2019) PLZ is available in Belgium as a magistral preparation from pharmacies who process the pharmaceutical material of PLZ in capsules (price: approx. €45 per 60 capsules). (C) In the United Kingdom, PLZ is available ('Nardil') from Neon Healthcare for £120 per 100 tablets (source: https://www.nice.org.uk/bnf, consulted on 30 October 2022). (D) In the United States of America, PLZ is available from Greenstone for $108.88 per 60 tablets (source: https://www.singlecare.com/prescription/phenelzine-sulfate, consulted on 30 October 2022). General speaking, the price of PLZ is much higher than other antidepressant drugs.

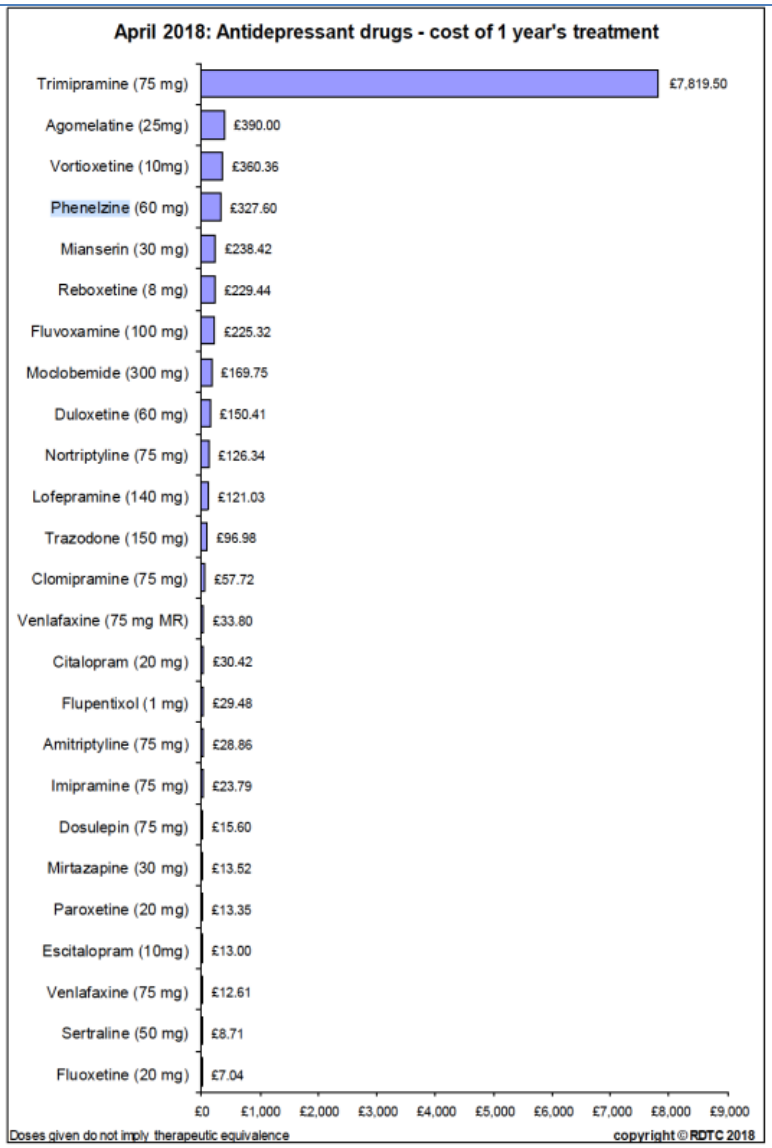

Table from Regional Drug and Therapeutics Centre (Newcastle)[79]

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:
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: