Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Notice of final decisions to not amend the current Poisons Standard in relation to ketamine, esketamine and methysergide.

19 October 2023

This document constitutes a notice of a final decision made by a delegate of the Secretary of the Department of the Health and Aged Care (the **Delegate**) under Regulation 42ZCZX in relation to proposed amendments to the current Poisons Standard which were not referred to an expert advisory committee under subdivision 3D.3 of the *Therapeutic Goods Regulations 1990* (the **Regulations**).

These final decisions follow three applications to amend the Poisons Standard in relation to ketamine, esketamine, and methysergide respectively on 2 and 3 March 2023.

Pursuant to r 42ZCZV of the Regulations, the Delegate made interim decisions to not amend the current Poisons Standard. On the 24 July 2023, the Delegate:

(a) made an interim decision on the applications having regard to the information provided by the applicant.
(b) provided the applicant a written notice setting out the interim decisions and the reasons for the decisions, and advised that they may, within the period specified in the notice (not being less than 10 business days after the date of the notice), make a written submission to the Delegate about the interim decisions.

No submission was received from the applicant within the specified period. Following this period of notice, the Delegate is making their final decisions to confirm their interim decisions in relation to ketamine, esketamine, and methysergide in accordance with r 42ZCZW of the Regulations.

In accordance with r 42ZCZX of the Regulations, this notice provides a publication of the Delegate's decision, and the reasons for the decision.

Proposals

Proposal in relation to ketamine and esketamine

The applicant proposed new Appendix D entries for ketamine and esketamine to apply when these substances are used for psychedelic-assisted psychotherapy (PAP). The new entries would restrict the prescribing of ketamine and esketamine for human therapeutic use during PAP to psychiatrists who had been authorised to do so by an appropriate authority, or as part of an approved clinical trial (the **ketamine and esketamine Proposals**).

The original applications were received on 3 March 2023. Additional information and clarification were sought from the applicant, who submitted revised applications on 14 March 2023.

Proposal in relation to methysergide

The applicant proposed to create a new Schedule 8 entry for methysergide when used in preparations for treatment during PAP. The proposal included additional Appendix D entries, consistent with the applications for ketamine and esketamine (as above) and those added to the Poisons Standard on 1 July 2023 for psilocybine and MDMA.

The new entry would restrict the prescribing of methysergide for human therapeutic use during PAP to psychiatrists who had been authorised to do so by an appropriate authority, or as part of an approved clinical trial (the **methysergide Proposal**).

Final decisions in relation to ketamine, esketamine and methysergide

Final Decisions

Pursuant to r 42ZCZW of the Regulations, a Delegate of the Secretary has made final decisions to not amend the current Poisons Standard in relation to ketamine, esketamine and methysergide.

Materials considered

In making this final decision, the Delegate considered the following material:

- The revised applications to amend the current Poisons Standard with respect to ketamine, esketamine, and methysergide (the **Applications**).
- Section 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (the **Act**), in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health.
- the Scheduling Policy Framework 2018 (the **SPF**),[1] and
- the Scheduling handbook: Guidance for amending the Poisons Standard (the **Handbook**).

Reasons for the final decisions (including findings on material questions of fact)

I have made the final decisions to confirm my interim decisions to not amend the current Poisons Standard with respect to ketamine, esketamine and methysergide. My reasons for making the final decisions are those set out in the interim decisions, as provided to the applicant under r 42ZCZV of the Regulations on 24 July 2023. These reasons are as follows.

Ketamine and esketamine

The basis of my decisions is that the substances meet the scheduling factors for inclusion in Schedule 8, as outlined in the SPF, and that additional controls on possession and supply through Appendix D are not required for any use, including those specified in the Applications.

The revised Applications in each case include proposals for separate entries in Schedule 8 for ketamine and esketamine, both when used during PAP and except when used during PAP. I consider this distinction to be redundant as it effectively covers all possible uses of the substance under the same Schedule, and therefore I have considered these applications on the basis that the existing Schedule 8 entries for each substance would not change under the respective proposals.

Instead, on considering each application in its entirety, I understand the applicant's intent to be the placement of additional Appendix D conditions when ketamine or esketamine are used as an adjunct to PAP. This would be achieved by including this condition in each of the proposed Appendix D entries, and I have proceeded with my considerations on this basis.

I have considered, pursuant to s 52E(1)(b) of the Act, that ketamine is a dissociative anaesthetic that is typically used in a medical setting to induce and maintain anaesthesia, but also has a history of off-

[1] Pursuant to paragraph 52E(2)(a) of the Act

label use in Australia for the treatment of depression. Ketamine's anaesthetic properties lend it to abuse by recreational users, and it is primarily for this reason that ketamine was up-scheduled to Schedule 8 in 2004. Esketamine, which is an enantiomer of ketamine, is used in nasal spray formulations for the treatment of depression and was included in Schedule 8 for similar reasons to ketamine.

The Applications seek to restrict the prescription of ketamine and esketamine, when used as adjuncts in PAP, to psychiatrists who have been authorised to do so under state or territory legislation, or in clinical trials. Effectively, these proposals seek to align the scheduling of ketamine and esketamine with the re-scheduling of psilocybine and MDMA, which came into effect on 1 July 2023. However, I emphasise that psilocybine and MDMA were down-scheduled from Schedule 9 to Schedule 8 only in specific circumstances, with additional controls applied to Schedule 8 use as instituted through Appendix D. Ketamine and esketamine are already considered to be appropriate for Schedule 8 without any such additional controls. I consider that the disparity in Appendix D entries is on its face insufficient to justify introducing additional controls on ketamine and esketamine.

I have proceeded to consider (i) whether there is sufficient information before me that persuades me, having regard to s 52E(1) of the Act, that the proposed Appendix D restrictions are warranted, and (ii) whether, pursuant to s 52E(2) of the Act, the proposed additional controls to the Schedule 8 substances are consistent with the SPF.

In relation to (i), the Applications note that medical practitioners are already prescribing ketamine as part of PAP in Australia. The Application implies that the risks associated with the use of ketamine and esketamine in the practice of PAP are, in the absence of the proposed restrictions in Appendix D, not currently mitigated. However, the Applications fail to demonstrate the risks of ketamine or esketamine when used in PAP to justify additional restrictions through Appendix D.

Turning my mind to (ii), the scheduling factors relating to Schedule 8 in the SPF include the recognition of the therapeutic value of the substance, countered by the potential for the development of dependency among users and a high propensity for misuse, abuse or illicit use. Consistent with the NDPSC decision in 2004, I consider that previous assessments of the benefits and risks of the substances are consistent with the existing Schedule 8 classification for ketamine and esketamine, without the requirement for additional controls. I note that the validity of the Schedule 8 classification of ketamine when used in medical settings outside of PAP is not disputed by the applicant.

As per the SPF, Appendix D provisions may be considered for any human or veterinary medicine where:

- a specific health risk that may be mitigated by restricting availability through specialist medical practitioners, or
- significant potential for illicit diversion and/or abuse which does not warrant inclusion in Schedule 8 but warrants particular control of possession, or
- a specific high potential for abuse, particular international treaty on restrictions on availability or other matters of national public health policy which when weighed against the need for access to the substance, warrants, in addition to inclusion of the substance in Schedule 4 or 8, further restrictions on access, such as authorisation by the Secretary of the Department of Health and Aged Care or some other appropriate State/Territory or Commonwealth authority.

I do not consider that any of these factors for Appendix D apply to ketamine. Similarly, for esketamine, there is no evidence that I am aware, in the Application or otherwise, that suggests that

the substance is being misused in this manner or presents an unwarranted health risk under the current provisions provided by a Schedule 8 classification.

I acknowledge the statement from the Royal Australian and New Zealand College of Psychiatrists (RANZCP), as cited in the Application, regarding the use of ketamine in psychiatric practice. The RANZCP memorandum indicates that ketamine should only be used by practitioners with appropriate expertise to do so. This aligns with the Schedule 8 classification.

As indicated above, it is important to recognise that psilocybine and MDMA continue to be primarily regarded as Schedule 9 substances. The potential for abuse and misuse of these substances, when weighed against the evidence of potential benefit to human health, is consistent with the SPF factors for Schedule 9. It is only under significantly restricted circumstances that these substances are being made available for therapeutic use. In making my decision to re-schedule psilocybin and MDMA, I considered that only practitioners of suitable expertise should be involved in prescribing, and only after being appropriately authorised to do so. This is due to the still-emerging evidence of the efficacy of the substances in treating specific mental health conditions, in addition to concerns regarding the potential for diversion and misuse.

By contrast, based on similar criteria, ketamine and esketamine have been previously considered solely as Schedule 8 medicines and I do not consider that there are appropriate grounds at this time to alter the terms of access by placing additional controls on these medicines. Therefore, I have made decisions not to amend the Standard with regards to ketamine and esketamine.

Methysergide

The basis of my decision is that methysergide does not meet the scheduling factors for inclusion in Schedule 8, as outlined in the SPF, and that Appendix D entries are not required for any use, including those specified in the Application.

Methysergide is a substance of the ergoline and lysergamide groups which has previously been used therapeutically for the prevention and treatment of migraine and cluster headaches.[2] However, with the development of newer, safer, and more efficacious medicines such as triptans, methysergide is no longer recommended as a first-line treatment for these indications by international peak bodies[3,4] and relevant public health societies.[5,6] There are presently no active products on the Australian Register of Therapeutic Goods (ARTG) that contain methysergide.[7]

The Application seeks to restrict the prescription of methysergide, when used as an adjunct in PAP, to psychiatrists who have been authorised to do so under state or territory legislation, or in clinical trials. Similar to the ketamine and esketamine Proposals, this application seeks to align the scheduling of methysergide with the re-scheduling of psilocybine and MDMA, which came into effect on 1 July 2023. The applicant proposes to do this by creating a new Schedule 8 entry for

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[2] Koehler, P. J., & Tfelt-Hansen, P. C., 2008. History of methysergide in migraine. *Cephalalgia*, *28*(11), pp. 1126-1135.

[3] Eigenbrodt, A.K., Ashina, H., Khan, S., Diener, H.C., Mitsikostas, D.D., Sinclair, A.J., Pozo-Rosich, P., Martelletti, P., Ducros, A., Lantéri-Minet, M. and Braschinsky, M., 2021. Diagnosis and management of migraine in ten steps. *Nature Reviews Neurology*, *17*(8), pp.501-514.

[4] Silberstein, S.D., Holland, S., Freitag, F., Dodick, D.W., Argoff, C. and Ashman, E., 2012. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*, *78*(17), pp.1337-1345.

[5] Therapeutic Guidelines tgldcdp.tg.org.au/etgAccess

[6] The state of migraine: An update on current and emerging treatments

[7] ARTG database www.tga.gov.au/artg

methysergide when used in PAP, with additional Appendix D controls that are analogous to those implemented for psilocybine and MDMA.

Methysergide was included in Schedule 4 (prescription only medicine) of the Poisons Standard by the Drugs and Poisons Schedule Committee in November 1988. The scheduling of methysergide has not been reconsidered since the original scheduling decision.

With regards to paragraph 52E(1)(b) and (e) of the Act, in addition to observing that there are no active registered therapeutic products in Australia that contain methysergide, I note further that there have been no applications to access the medicine through the TGA's Special Access Scheme since 2013. I consider this to be significant given that Deseril, the only product containing methysergide on the ARTG, was removed from the register in 2017, which indicates that the overall demand for the substance for any therapeutic use is now negligible or non-existent. Based on this information, I consider that there is minimal risk to public health from any therapeutic use of methysergide as a medicine in Australia. While the volume of use of a substance, or lack thereof, does not in itself preclude its up-scheduling, I consider this to be a relevant factor in assessing the overall risks to public health from use of the substance as outlined in the Application.

With reference to the SPF, I have considered whether methysergide may align with any or all of the factors for a Schedule 8 substance. Methysergide is not included in either the United Nations Single Convention on Narcotic Drugs 1961[8] or the United Nations Convention on Psychotropic Substances 1971.[9] Further, and with additional consideration to section 52E(1)(d) of the Act, I see no evidence in the Application or otherwise that methysergide produces dependency or a propensity for misuse, abuse or illicit use. Therefore, I do not consider that methysergide aligns with the SPF factors for a Schedule 8 medicine, and the existing Schedule 4 classification of the medicine places appropriate controls on its use.

As outlined in the decision for ketamine and esketamine above, it is important to recognise that psilocybin and MDMA were down-scheduled from Schedule 9 to Schedule 8 with significant restrictions after weighing their therapeutic values in treatment-resistant depression or post-traumatic stress disorder, and the high risk of abuse and misuse associated with these substances.

I emphasise that the scheduling decisions in relation to psilocybine and MDMA are in contrast with the proposed changes by the applicant, whose intention is to up-schedule methysergide from Schedule 4 to Schedule 8, with further additional controls through Appendix D when prescribing for certain indications. I find there is insufficient evidence to support increased restrictions to this substance as the applicant has failed to demonstrate the risks associated with the substances when used in PAP, and has not indicated that the current scheduling is inadequate according to the SPF factors.

Based on the above reasons, I am of the opinion that the existing scheduling entries for ketamine, esketamine, and methysergide, are appropriate and align with the relevant factors listed in the SPF. I am also of the opinion that the applications did not provide evidence that the risk of these substances, when used in PAP or otherwise, has changed since the substances were last considered for scheduling. Therefore, I have decided not to amend the Standard with respect these substances.

[8] United Nations Single Convention on Narcotic Drugs 1961 www.unodc.org/pdf/convention_1961_en.pdf

[9] United Nations Convention on Psychotropic Substances 1971 www.unodc.org/pdf/convention_1971_en.pdf

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