Australian Government
Department of Health
Therapeutic Goods Administration

Ratified Record of the 32nd meeting of the Advisory Committee on Medicines Scheduling

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TGA Health Safety Regulation

Contents

[redacted]

2.3 Psilocybin

Advice for the delegate's consideration

The Committee advised that the current scheduling of psilocybin remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health.

- The Committee recommended that psilocybin does not meet the Schedule 8 Scheduling Factors, noting that:
  - It is an illicit drug, included in Schedule I of the United Nations Convention on Psychotropic Substances.
  - Its therapeutic value has not yet been established, with clinical trials ongoing.
  - Its potential for misuse is significant and at present, the benefits of use are substantially outweighed by the risks.
- The Committee noted that evidence regarding the safety and efficacy of psilocybin-assisted psychotherapy is still emerging; phase II trials are currently underway, and phase III trials are registered. The medium and long term effects of such therapy are unknown. The committee was of the view that down-scheduling at this time is premature and a larger body of evidence is needed to support such a change, noting that while early studies have reported high remission rates, they lack appropriate control groups.
- Members were of the view that maintaining the Schedule 9 entry for now, would ensure the continued provision of quality clinical data.
- Members noted that:
  - A recent review in *the American Journal of Psychiatry* concluded that, although research is promising, the overall database is insufficient for regulatory approval for clinical use.
  - The applicant emphasised that psilocybin has been granted two 'Breakthrough Therapy Designations' by the FDA in the USA. The Committee noted that, while these designations indicate that the therapy shows promise, they do not equate to FDA approval. The US scheme for trial use of the drug is broadly similar to the Australian SAS-B scheme.
  - There is no international framework for how to handle psychedelic-assisted therapies, and no comparable country has down-scheduled psilocybin to an equivalent category to Schedule 8.
- The Committee considered the 575 responses were received in the pre-meeting consultation:
  - 553 were supportive of the proposed amendment, 11 partially supportive and 11 opposed. A large proportion of the supportive submissions paraphrased the sponsor, and few were from practicing psychiatrists.
  - The Royal Australian and New Zealand College of Psychiatrists advised that further research is required to assess the efficacy, safety, and effectiveness of psychedelic therapies, emphasising that appropriate treatment methodologies and training protocols do not yet exist. The Committee unanimously agreed that these pathways should be developed prior to down-scheduling.
  - It was noted that although a large proportion of the population have mental health conditions, relatively few have conditions which are refractory to existing available treatments.

- The Australian Medical Association advised that more high-quality research, using larger-scale studies, is required to establish the safety and efficacy of psychedelic therapies. The risk of psychosis and persistent hallucinations, especially in susceptible subpopulations, is likely to be high.
- The committee queried supporters' assertions that down-scheduling would reduce costs and that access to the drug is extraordinarily difficult. The paperwork for Commonwealth and State approval of access for clinical trials is fast and straightforward. There is a current trial under way at St Vincent's Hospital Melbourne.

- The committee advised that the current spelling of the Schedule 9 entry remains appropriate, noting that the spelling "psilocybine" is consistent with the International Nonproprietary Name and British Approved Name of the substance.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Benefits:

- There is limited but emerging evidence that psychedelic therapies may have therapeutic benefits in the treatment of a range of mental illnesses. These benefits are currently under investigation in clinical trials.

Risks:

- There remain many unknown factors and side effects, especially in the long term. The risks of developing psychosis, especially in vulnerable populations, must be established in a clinical trial setting.
- Can cause tachycardia and transient increases in blood pressure.
- Psilocybin, when misused, can caused psychosis.

b) the purposes for which a substance is to be used and the extent of use of a substance

- Psilocybin is taken in combination with psychotherapy for the treatment of depression, PTSD, anxiety, or end of life distress.
- Psilocybin-assisted psychotherapy sessions typically last 6 – 8 hours, relying on two trained specialists. The regime consists of 1 – 3 psychedelic-assisted therapy sessions, usually supplemented with 'integrative' therapy sessions where psilocybin is not used.

c) the toxicity of a substance

- The lethal dose is thought to be 6 g, although evidence around toxicity may be premature.
- The potential adverse effects, particularly relating to multi-drug toxicity, are unknown.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- A typical dose in the context of psychotherapy is 25 – 35 mg, depending on subject weight. An optimal therapeutic dosage has not been established.

e) the potential for abuse of a substance

- There is a high risk of diversion for misuse, even in conjunction with Schedule 8 controls.

f) any other matters that the Secretary considers necessary to protect public health

- There are significant benefits to waiting for the results of clinical trials. Psilocybin-assisted psychotherapy may eventually prove to be safe and efficacious, but the evidence does not yet suggest this.
- It will take years to develop a curriculum and accredited training process for psychiatrists. To protect public health and prevent misuse, psilocybin should not be down-scheduled until all necessary safeguards have been established and implemented.

2.4 MDMA

Advice for the delegate's consideration

The Committee advised that the current scheduling of MDMA remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health.

- The Committee recommended that MDMA does not meet the Schedule 8 Scheduling Factors, noting that:
  - It is an illicit drug, included in Schedule I of the United Nations Convention on Psychotropic Substances.
  - Its therapeutic value has not yet been established, with only Phase II trial results currently available.
  - Its potential for misuse is significant and at present, the benefits of use are substantially outweighed by the risks.
- The Committee noted that evidence regarding the safety and efficacy of MDMA-assisted psychotherapy is still emerging. Several phase II trials have been completed, but these lack rigorous control groups. Higher-quality data is required to establish efficacy; a single phase III trial has been completed but the results have not yet been published. The medium and long term effects of such therapy are not well described.
- The committee noted that MDMA does not have an established therapeutic value although there is evidence from phase II clinical trials that it has benefit in PTSD in association with psychotherapy. There is no evidence for any therapeutic value outside of this indication and evidence for this is also limited due to small sample sizes and difficulty in blinding patients.
- The committee also raised that it was unclear as to whether MDMA is addictive, noting that it affects many of the same neurotransmitter systems in the brain that are targeted by other addictive drugs, and some studies report symptoms of addiction in users.
- Members noted that prolonged, even intermittent, use can result in sleep disturbances, difficulties with concentration, depression, heart disease, impulsivity and decreased cognitive function. It can also reduce the ability to perceive and predict motion and can therefore result in accidents.
- Members noted that:

  - A recent review in *Progress in Neuro-Psychopharmacology and Biological Psychiatry* concluded that, while MDMA-assisted psychotherapy appears to be safe and effective, more research is needed – with larger sample sizes and longer durations of treatment.
  - MDMA-assisted psychotherapy has been granted 'Breakthrough Therapy Designation' by the FDA in the USA. The Committee noted that, while this designation indicates that the therapy shows promise, it does not equate to FDA approval. The US scheme for trial use of the drug is broadly similar to the Australian SAS-B scheme.
  - There is no international framework for how to handle psychedelic-assisted therapies, and no comparable country has down-scheduled MDMA to an equivalent category to Schedule 8.

- One Committee member noted that there may be an unmet need for a population of treatment-resistant PTSD patients, especially when electroconvulsive therapy is not appropriate. However, there was a consensus that the harms to an early downscheduling decision would outweigh the potential benefits at this time. A large proportion of the population have mental health conditions, but relatively few have conditions which are refractory to existing available treatments.
- The Committee noted that individuals can currently apply for MDMA-assisted therapy, through the SAS-B scheme, outside of Queensland and the ACT – although these applications are unlikely to gain approval outside of a clinical trial setting.
- The Committee discussed the applicant's concerns regarding research barriers and noted that clinical trials for MDMA-assisted psychotherapy are currently possible in all Australian states and territories except for Queensland (QLD). The QLD state member clarified that clinical trial access would soon be possible following an upcoming change to QLD poisons legislation.
- MDMA is subject to significant illicit use in the Australian community resulting in harms including deaths.
- The Committee noted the 478 consultation responses consultation:
  - 453 were supportive of the proposed amendment, 14 partially supportive and 11 opposed. A large proportion of the supportive submissions paraphrased the sponsor, and few were from practising psychiatrists.
  - The Royal Australian and New Zealand College of Psychiatrists advised that further research is required to assess the efficacy, safety, and effectiveness of psychedelic therapies, emphasising that appropriate treatment methodologies and training protocols do not yet exist. The committee unanimously agreed that these pathways should be developed prior to downscheduling.
  - The Australian Medical Association advised that more high-quality research, using larger-scale studies, is required to establish the safety and efficacy of psychedelic therapies. The risk of psychosis, especially in susceptible subpopulations, is likely to be high.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Benefits:

- There is limited but emerging evidence that MDMA-assisted psychotherapy may have therapeutic benefits in the treatment of PTSD. These benefits are currently under investigation in clinical trials.

Risks:

- Acute effects include high blood pressure and pulse rate, faintness and panic attacks. In severe cases, MDMA can cause loss of consciousness and seizures.
- Secondary effects include involuntary jaw clenching, lack of appetite, depersonalisation, illogical or disorganised thoughts, restless legs, nausea, hot flashes or chills, headache, sweating and muscle/joint stiffness.
- Long-term use can result in sleep disturbances, difficulties with concentration, depression, heart disease, impulsivity and decreased cognitive function.
- MDMA can reduce the ability to perceive and predict motion and can therefore result in accidents.

b) the purposes for which a substance is to be used and the extent of use of a substance

- MDMA is taken in combination with psychotherapy for the treatment of PTSD.
- MDMA-assisted psychotherapy sessions typically last 6 – 8 hours, relying on two trained specialists. The regime consists of 1 – 3 psychedelic-assisted therapy sessions, usually supplemented with 'integrative' therapy sessions where MDMA is not used.

c) the toxicity of a substance

- The lethal dose is 10 – 20 mg/kg.
- The potential adverse effects are unknown in the context of psychotherapy.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- Optimal dosages have not been established, especially outside of PTSD treatment.
- A typical dose in the context of psychotherapy is 1-2 mg. This is often followed by an optional half-dose 1.5 to 2.5 hours into the session.

e) the potential for abuse of a substance

- It is not clear whether MDMA causes dependence. However, it affects many of the same neurotransmitter systems in the brain that are targeted by drugs with an abuse and dependence liability, and some studies report symptoms of dependence in users.
- There is a high risk of diversion for misuse, even in conjunction with Schedule 8 controls.

f) any other matters that the Secretary considers necessary to protect public health

- There are significant benefits to waiting for the results of clinical trials. MDMA-assisted psychotherapy may prove to be safe and efficacious, but the evidence does not yet suggest this – especially for conditions outside of PTSD.
- It will take time to develop a curriculum and accredited training process for psychiatrists. To protect public health and prevent inappropriate use, MDMA should not be down-scheduled until all necessary safeguards have been established and implemented.