Etizolam:
Report to the Expert Advisory Committee on Drugs

Prepared by the Ministry of Health

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Contents

1 EXECUTIVE SUMMARY

Etizolam is a central nervous system depressant and classified as a benzodiazepine derivative. In New Zealand, all benzodiazepine derivatives are classified as prescription medicines under the Medicines Regulations 1984. Etizolam is not currently classified as a controlled drug.

High or over-dosing of etizolam can result in adverse effects similar to other benzodiazepines. These include sedation, sleepiness, muscle relaxation, ataxia, slurred speech and loss of consciousness. Motor and functional impairment was diagnosed in adults with high doses of etizolam found in their blood samples. In most cases with etizolam-related overdosing and toxicity, they occurred in poly-drug scenarios, with high dosages of many other drugs taken simultaneously.

In recent years, there has been an increase in the number and availability of new benzodiazepine products on illicit drug markets across Europe, Canada and the United States. Etizolam was one of two substances that notably dominated as a new benzodiazepine product being used and distributed illicitly in Europe. Non-medical use of etizolam has been indicated in many countries following the increase in prevalence of 'designer' benzodiazepines readily available on the illicit market. There is significant emerging evidence of non-medical use of etizolam and harms relating to abuse. United Kingdom, Canada, Denmark and Germany have all scheduled etizolam under legislation to restrict use and abuse of etizolam in their local drug markets. Etizolam was the third most frequently detected substance reported among all drug-related deaths in 2016, contributing to 46% of all drug-related deaths in Scotland in 2018. Dependence potential has been demonstrated in humans, with many users reporting tolerance, craving and withdrawal following use of etizolam.

On 3 November 2020, etizolam was placed under international control and scheduled under Schedule IV of the Convention on Psychotropic Substances 1971 following a recommendation from the WHO Expert Committee on Drug Dependence (ECDD).

The Minister of Health issued a temporary class drug order (TCDO) for etizolam on 17 February 2022 following a request from the National Drug Intelligence Bureau (NDIB) in June 2021.

NDIB data showed there were increasing levels of etizolam being seized by NZ Customs from 2017 to 2020. Looking at overseas trends of use and abuse of etizolam, it is likely that this drug could become a substance of abuse in the New Zealand illicit market. KnowYourStuffNZ have also identified a small number of samples containing etizolam. The street value for etizolam is approximately 50 cents per 2 mg dose, making this substance highly attractive to vulnerable population groups.

2 INTRODUCTION

2.1 Purpose

This report provides an overview of etizolam and options for scheduling recommendations under the Misuse of Drugs Act 1975.

2.2 Substance classification

Etizolam is classified as a benzodiazepine derivative. All benzodiazepine derivatives are currently classified as prescription medicines under the Medicines Regulations 1984. Etizolam is not currently classified as a controlled drug.

2.3 Why is this substance being considered?

Etizolam is to be considered by the Expert Advisory Committee on Drugs (EACD) as there has been a temporary class drug order (TCDO) issued for etizolam following a request from the National Drug Intelligence Bureau (NDIB) in June 2021 (NDIB TCDO request available in the appendix). The TCDO came into force on 17 February 2022, and as a requirement of section 4E of the Misuse of Drugs Act 1975, etizolam must be reviewed by the EACD to provide advice on the scheduling of this drug to the Minister (https://www.legislation.govt.nz/act/public/1975/0116/latest/LMS239794.html).

A request for a TCDO for etizolam was submitted by NDIB after increasing evidence of seizures of etizolam in the recent years which may potentially pose a risk to New Zealand society. NDIB data showed there was increasing levels of etizolam being seized by NZ Customs from 2017 to 2020. Looking at overseas trends of use and abuse of etizolam, it is likely that this drug could become a substance of abuse in the New Zealand illicit market.

On 3 November 2020, etizolam was placed under international control and scheduled under Schedule IV of the Convention on Psychotropic Substances 1971 following a recommendation from the WHO Expert Committee on Drug Dependence (ECDD). It was considered there was sufficient evidence of abuse of etizolam to constitute a public health and social problem at their 42nd meeting (WHO 2019). New Zealand is a signatory to this Convention and therefore has an obligation to consider etizolam for scheduling under domestic legislation.

3 SUBSTANCE IDENTIFICATION AND CHEMISTRY

3.1 Identification

IUPAC Name: 4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2f][1,2,4] triazolo[4,3-α][1,4]diazepine

CAS Number: 40054-69-1

Molecular weight: 342.845 g mol^{-1}

Molecular formula: $C_{17}H_{15}ClN_4S$

Appearance: White powder

Solubility: Not soluble in water. Soluble in acidic water, polyethylene glycol, ethanol, methanol and chloroform

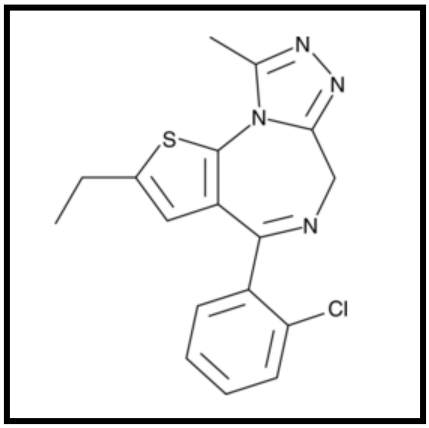


Figure 1: Chemical structure of etizolam

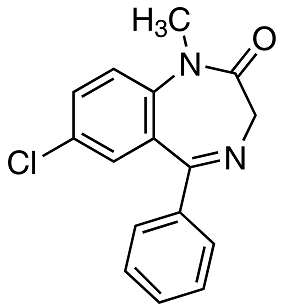
3.2 Therapeutic value

The therapeutic uses of etizolam include the treatment of anxiety, depressive disorders and insomnia. Currently, the only countries which have approved uses of etizolam as a prescription medicine are Japan, Italy and India (WHO 2019; EMCDDA 2021; ACMD 2016).

In New Zealand, benzodiazepine derivatives are scheduled as prescription medicines under the Medicines Regulation 1984. However, there are no approved products containing etizolam in New Zealand. Doctors can prescribe etizolam under section 25 of the Medicines Act 1981 which permits authorised prescribers to procure, administer or arrange the administration of an unapproved medicine, but this is not subsidised.

3.3 Similarities to Other Known Substances

Diazepam



Diazepam is indicated for short term severe anxiety, anxiety disorders, tension headaches, symptoms of alcohol withdrawal, muscle spasms and the management of some types of epilepsy. The administered dose varies depending on the indication, and typically ranges between 2 to 30 mg per day. It has a half-life up to 48 hours, which is significantly greater than that of etizolam (U.S. FDA 2016; Medsafe 2019).

Diazepam is a scheduled under Part 5 of Schedule 3 (Class C) in the Misuse of Drugs Act 1975 (https://www.legislation.govt.nz/act/public/1975/0116/latest/DLM436723.html?search=sw_096be8ed81ba0494_diazepam_25_se&p=1&sr=0).

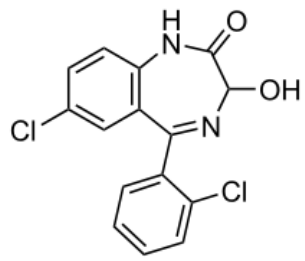
Comparing etizolam to diazepam

Etizolam is approximately 6-10 times more potent than diazepam for its pharmacological effects. These include anxiolytic, anti-convulsant, sedative-hypnotic and muscle relaxant effects. The LD_{50} of etizolam is reported to be 2-5 times higher than that of diazepam. Etizolam is shown to be less lethal when compared to diazepam as 1 mg of etizolam is equivalent to 5 mg of diazepam (WHO 2019).

Structural comparison of etizolam and diazepam

Diazepam has a benzodiazepine core structure. Comparatively, etizolam has a thienodiazepine core fused with a benzene ring structure.

Lorazepam



Lorazepam is indicated for the treatment of moderate to severe anxiety and insomnia associated with anxiety. Dosing may range from 1 to 10 mg per day. Conventional dosing ranges between 1 to 3 mg per day. It has a half-life of 12-16 hours (Medsafe 2017).

Lorazepam is scheduled under Part 5 of Schedule 3 (Class C) in the Misuse of Drugs Act 1975 (https://www.legislation.govt.nz/act/public/1975/0116/latest/DLM436723.html?search=sw_096be8ed81ba0494_lorazepam_25_se&p=1&sr=0).

Comparing etizolam to lorazepam

Etizolam is less likely to induce dependence when compared to lorazepam. This was demonstrated in animal studies which compared different benzodiazepines using *in vivo* dependence studies (WHO 2019).

Structural comparison of etizolam and lorazepam

Etizolam and lorazepam both have a benzene ring fused to the core structure with a chlorine attached to the second carbon. As lorazepam is a benzodiazepine, it has a benzodiazepine core, which differs from the thienodiazepine core present in etizolam.

3.4 Methods and ease of manufacturing

Etizolam is manufactured in several laboratories for both clinical and research purposes. Etizolam is manufactured through a cyclisation reaction from a precursor substance to create the triazol-benzodiazepine derivative. This can be facilitated from a catalytic amount of p-tolene sulphonic acid with the precursor benzodiazepine leading to cyclisation and the synthesis of a triazol-benzodiazepine derivative (WHO 2019; EMCDDA 2021).

It can also be produced from the cleavage of the keto group of a precursor benzodiazepine, and formation of the triazol ring through cyclisation of an acetyl hydrazone derivative, creating a triazol-benzodiazepine derivative. These chemical reactions are outlined in patents US8106189 B2 and WO 2009/069147 A3 (WHO 2019; Google Patents 2007; PATENTSCOPE 2009).

Evidence suggests that the majority of the etizolam available in the European illicit market has been produced and sourced from small scale laboratories and pharmaceutical companies in India as the finished product form (EMCDDA 2021; Reddit 2021a). Other illicit manufacture is facilitated through the importation of bulk etizolam powder from laboratories in China. It then undergoes production through pill-pressing machines and packaging before it is distributed into the local illicit drug market. This has been demonstrated in Scotland, as etizolam has been identified as the predominant benzodiazepine abused (WHO 2019; Daily Record 2021a). Large

scale production of illicit etizolam tablets has also been seen in Scotland. Equipment that has been seized by Police was thought to be able to produce 180,000 pills an hour (WHO 2019; Daily Record 2021b).

4 RISK OF HARM

4.1 Likelihood or Evidence of Abuse in New Zealand

Seizure data from New Zealand Customs Service suggests that some etizolam is present in the illicit drug market of New Zealand. In 2021, 1115 pills, tablets or capsules were seized by New Zealand Customs Service. KnowYourStuffNZ have also identified a small number of samples containing etizolam. The street value for etizolam is approximately 50 cents per 2 mg dose, making this substance highly attractive to vulnerable population groups. There is also evidence that etizolam is circulating through darkweb marketplaces and social media platforms within New Zealand (NDIB TCDO request available in appendix).

Recently, there has been an increase in the number and availability of new benzodiazepine products on illicit drug markets across Europe, Canada and the United States. Etizolam was one of two substances that notably dominated as a new benzodiazepine product being used and distributed illicitly in Europe. These developments in these jurisdictions have given rise to concern for individual and public health (EMCDDA 2021, ACMD 2016). Non-medical use of etizolam has been indicated in many countries following the increase in prevalence of ‘designer’ benzodiazepines readily available on the illicit market (WHO 2019).

Many illicit etizolam users have been seen in polydrug-use settings, including in opioid users. Frequent and excessive use of benzodiazepines has been demonstrated to be used to enhance or prolong the effects of other drugs and to avoid unwanted withdrawal symptoms (EMCDDA 2021). Restrictions for prescribing benzodiazepines may lead to some users relying on illicit benzodiazepines or derivatives to self-medicate for indications such as insomnia or anxiety (EMCDDA 2021).

These trends are important to note in case there is a large increase of etizolam availability in the New Zealand drug market as seen in many overseas countries. This is particularly notable for vulnerable populations who may already be susceptible to drug use.

New Zealand seizure data

The National Drug Intelligence Bureau (NDIB) advised of seizures shown in table 1.

Table 1: Seizure quantities by Police and Customs of Etizolam 2017-2021

2021	2020	2019	2018	2017
Total quantity seized (pills, tablets, capsules)	Total quantity seized (pills, tablets, capsules)	Total quantity seized (pills, tablets, capsules)	Total quantity seized (pills, tablets, capsules)	Total quantity seized (pills, tablets, capsules)
1115.0	2765.5	830.0	1452.5	1127.2

4.2 General Pharmacology

Etizolam is a central nervous system depressant which leads to anxiolytic effects, sedation, muscle relaxation, anticonvulsant effects and sleep-inducing effects. This is regulated through the modulation of the GABA receptors leading to inhibition of neurotransmitters on the pre- and post-synaptic terminal and consequently causing down-regulation of receptors in the central nervous system (EMCDDA 2021; WHO 2019).

Routes of Administration and Dosage

Etizolam is mainly administered orally in a tablet form. Other less common administration routes include intravenously, intramuscular injection, rectal administration, snorting and smoking/vaping (WHO 2019; EMCDDA 2021). Other forms that etizolam has been presented in include capsules, blotters and e-liquids (Brunetti et al 2021; EMCDDA 2021).

Usual clinical dosing can range from 0.5 to 2 mg per day, with a maximum of 3 mg per day (WHO 2019). Illicit dosing varies between 1.5 to 7 mg per day depending on the desired outcome of the user (Reddit 2021c).

Pharmacodynamics

Etizolam acts similarly to other benzodiazepines by causing central nervous system depression through targeting the central $GABA_A$ receptors located on the post- and presynaptic membranes. As $GABA_A$ is a ligand-gated ion channel, receptor activation leads to hyperpolarisation and inhibition of neurotransmission (EMCDDA 2021).

Etizolam allosterically potentiates chloride currents induced by GABA in $GABA_A$ receptors. This inhibitory effect on the central nervous system leads to anxiolytic, anti-convulsant, sleep-inducing or muscle relaxant effects depending on the location of the receptor (WHO 2019; DRUGBANK Online 2021).

Pharmacokinetics

Etizolam is metabolised in humans through microsomal oxidation at its methyl and ethyl groups. Cytochrome P450 CYP3A4 and CYP2C19 enzymes are involved in its metabolism. The hydroxylated derivatives of etizolam are conjugated and excreted. Etizolam has a half-life of around 5 to 7 hours and is classed as a short-acting benzodiazepine. Peak effects from etizolam can be experienced from 0.5 to 2 hours after oral administration (WHO 2019; EMCDDA 2021).

Drug interactions which may impact the metabolism of etizolam include those that modulate CYP enzyme activity. CYP inhibitors or inducers may impact the metabolism and excretion of etizolam (WHO 2019; EMCDDA 2021).

4.3 Toxicology

High or over-dosing of etizolam can result in adverse effects similar to other benzodiazepines. These include sedation, sleepiness, muscle relaxation, ataxia, slurred speech and loss of consciousness (WHO 2015). Motor and functional impairment was diagnosed in adults with high doses of etizolam found in their blood samples (Brunetti et al 2021). In most cases with etizolam-related overdosing and toxicity, they occurred in poly-drug scenarios, with high dosages of many other drugs taken simultaneously (Neilsen and McAuley 2020).

In the illicit market, specific dosages of etizolam may not be known due to poor illicit manufacturing processes leading to increased risk of overdosing in individuals. This increases the risk of unwanted adverse effects. This risk is heightened when taken in conjunction with other central nervous system depressant drugs (EMCDDA 2021; Brunetti et al 2021).

4.4 Risk to Public Health

The use of ‘designer’ benzodiazepines has been increasing, with etizolam presenting as one of the most common single agent exposures in a US study of poison calls. The reason for exposure to etizolam for most of the calls were due to abuse or misuse (WHO 2019). Etizolam has also become the predominant benzodiazepine abused in the illicit drug market in Scotland (EMCDDA 2021). Scottish prisons have also seen an 18-fold increase in street benzodiazepines which most commonly contain etizolam, and it is becoming one of the dominant drugs smuggled and used within their prisons (BBC Scotland News 2021).

There is significant emerging evidence of non-medical use of etizolam and harms relating to abuse (WHO 2019; Reddit 2021c).

Adverse events associated with etizolam include drowsiness and muscle weakness. It may also cause similar adverse effects characteristic to classical benzodiazepines

which include sedation, sleepiness, muscle relaxation, ataxia, slurred speech and loss of consciousness (WHO 2019).

4.5 Potential to Cause Death

Etizolam has been indicated in a number of deaths globally. In Scotland, from 2015 – 2019 the street benzodiazepines percentage of drug-related deaths increased from approximately 10% to over 60% (Scottish Drug Deaths Taskforce 2021). Etizolam was the third most frequently detected substance reported among all drug-related deaths in 2016, contributing to 46% of all drug-related deaths in Scotland in 2018 (WHO 2019). Etizolam resulted in the majority of Scotland's 1339 drug-related deaths in 2020 (Daily Record 2021).

It has been described that a case with a blood concentration of 264 ng/mL of etizolam may have been causal and contributed to death (WHO 2019). In many fatal instances, etizolam has been detected with other drugs often leading to multidrug intoxication (WHO 2019). In another case where 86 ng/mL of etizolam was detected in conjunction with high concentrations of another central nervous system depressant, it was seen that the combination of these drugs were causal for death (WHO 2019).

4.6 Potential for Physical or Psychological dependence

Dependence potential has been demonstrated in humans, with many users reporting tolerance, craving and withdrawal following use of etizolam (WHO 2019; Reddit 2018). However, evidence shows that it may have a lower ability to induce tolerance compared to other benzodiazepines. Therefore, increased dosages of etizolam may not be required over time to induce desired pharmacological effects (WHO 2019; EMCDDA 2021).

Tolerance and withdrawal symptoms are common to develop for benzodiazepines, shown through studies where self-administration of drugs was maintained reinforcing dependence (EMCDDA 2021; Reddit 2018).

Illicit users have readily reported withdrawal symptoms similar to other benzodiazepines following prolonged periods of high dosing (Reddit 2018). Tamburin *et al*. (2020) provided a neuropsychiatric evaluation in one patient who used high dose etizolam (15 mg/day). This report demonstrated the patient had deficits in working memory, visuospatial memory and executive function, which suggested high dose etizolam may result in negative cognitive side effects.

5 CLASSIFICATION

5.1 New Zealand Classification and Regulation

Etizolam is classified as a benzodiazepine derivative and is currently regulated as a prescription medicine under the Medicines Regulations 1984.

5.2 International Classification and Regulation

Australia

Benzodiazepine derivatives are listed in Schedule 4 (prescription medicine only) of the Poisons Standard (SUSMP). Etizolam is not currently considered a controlled drug.

United Kingdom

Etizolam has been classed as a Class C drug under the Misuse of Drugs Act 1971 since 2017 following the Misuse of Drugs Act (Amendment) Order 2017.

United States

Etizolam is not currently regulated as a controlled drug in the United States under the Federal Controlled Substances Act. However, some states have regulated etizolam as a controlled substance under Schedule I including Louisiana, Mississippi and Texas. Other states including Georgia and Arkansas have regulated etizolam as a controlled substance under Schedule IV (WHO 2019).

Canada

Etizolam is scheduled under Schedule IV of the Controlled Drugs and Substances Act 1996 as a benzodiazepine derivative.

Denmark

Etizolam is on list E of controlled substances outlined in the list of euphoriant substances only to be used for medical and scientific purposes.

Germany

Etizolam has been regulated as a controlled drug under the German Federal Narcotics Act since 2013.

5.3 UN Classification

Etizolam has been scheduled under Schedule IV of the 1971 Convention on Psychotropic Substances at the 63rd session after consideration and recommendation from the 42nd meeting of the ECDD. Substances listed in Schedule IV of the Convention are substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have a therapeutic usefulness from little to great.

6 OTHER RELEVANT INFORMATION

6.1 Background and History

Etizolam was developed in Japan to be used as an anxiolytic medicine in 1984. It is currently still used as a prescription medicine in Japan, Italy and India (WHO 2015).

6.2 Anticipated Future Trends

It is difficult to anticipate future trends for etizolam in New Zealand as there is limited New Zealand specific data on use and abuse. However, data from other jurisdictions suggest if etizolam did increase in local availability, there is potential for abuse and dependence in vulnerable populations, including those with known drug use and abuse.

7 CLASSIFICATION OPTIONS

Option 1 – Maintain status quo

Etizolam would remain a prescription medicine under the Medicines Regulations 1984. The period of supply would remain at 3 months per prescription. Etizolam can currently be prescribed by a doctor as an unapproved medicine. Prescribers or pharmacists may import unapproved medicines directly for their patients, at their own expense.

Anyone caught in possession of a prescription medicine (without a prescription) for personal use faces three months imprisonment and/or a $500 fine. Anyone (other than those exempted under the Medicines Act) convicted of selling or supplying a prescription medicine faces up to six months imprisonment or a fine not exceeding $20,000.

Option 2 – Schedule as a Class A controlled drug under the Misuse of Drugs Act 1975

Substances posing a very high risk of harm to individuals or society that are highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse. These substances generally have very little to no therapeutic value.

There may be additional implications for substances that are captured as an analogue of etizolam.

The regulatory penalties for Class A controlled drugs are listed below in Table 2. For a full breakdown on the controls, please see the EACD guidelines.

Option 3 – Schedule as a Class B controlled drug under the Misuse of Drugs Act 1975

Substances posing a high risk of harm to individuals or society that can be highly addictive and liable to abuse, or are easily convertible into drugs that are similarly

addictive and liable to abuse. These substances can have little to moderate therapeutic use.

There may be additional implications for substances that are captured as an analogue of etizolam.

The penalties for Schedule 2 (Class B) controlled drugs are listed below in Table 2. For a full breakdown of the differences in control between these parts of Schedule 2, please see the EACD guidelines.

Option 4 – Schedule as a Class C controlled drug under the Misuse of Drugs Act 1975

Substances posing a moderate risk of harm to individuals or society and a moderate to high risk of abuse and dependency or are easily convertible into drugs that are similarly addictive and liable to abuse. These substances can have little to great therapeutic use.

There may be additional implications for substances that are captured as an analogue of etizolam.

The penalties for Schedule 3 (Class C) controlled drugs are listed below in Table 2. For a full breakdown of the differences in control between these parts of Schedule 3, please see the EACD guidelines.

Etizolam has been scheduled under Schedule IV of the 1971 Convention on Psychotropic Substances. By scheduling etizolam as a Class C controlled drug under the Misuse of Drugs Act 1975, this would align with the scheduling under this UN convention.

Table 2: Comparison of penalties under the Misuse of Drugs Act

	Schedule 1 Class A Drugs	**Schedule 2 Class B Drugs**	**Schedule 3 Class C Drugs**	**Psychoactive Substances Act**
Importation, manufacture, or supply	Life imprisonment (subject to presumption of supply)	Up to 14 years imprisonment (subject to presumption of supply)	Up to 8 years imprisonment	Up to 2 years imprisonment (for individuals) or a fine not exceeding $500,00 (for a body corporate)
Conspiracy to commit an offence	Up to 14 Years imprisonment	Up to 10 years imprisonment	Up to 7 years imprisonment	N/A
Possession	Up to 6 months imprisonment or $1,000 fine or both	Up to 3 months imprisonment or $500 fine or both	Up to 3 months imprisonment or $500 fine or both	A fine not exceeding $500

8 PRESUMPTION FOR SUPPLY

8.1 Dosing

Licit dosing of etizolam ranges between 0.5 to 2 mg per day, and illicit dosing ranges from 1.5 mg to 7 mg per day (WHO 2019; Reddit 2021c).

Etizolam is mainly administered orally through a tablet form however, it can also be administered intravenously, as well as less common methods such as intramuscular injection and snorting (WHO 2019; EMCDDA 2021).

8.2 LD_{50}

LD_{50} is the abbreviation for “lethal dose, 50 percent”. It is the amount of an ingested substance that kills 50 percent of a test population.

It has been demonstrated in mice that the median lethal dose was 4300 mg/kg when administered orally. In rats, it was seen that the LD_{50} was 3550 mg/kg. When administered orally, the LD_{50} for etizolam is much higher than that of diazepam making etizolam less lethal (WHO 2019).

8.3 Legal possession

As etizolam is a prescription medicine it could be imported with a prescription for a patient in New Zealand by an authorised medical practitioner.

Assuming that the maximum clinical dose is 3 mg per day as per overseas clinical dosing, and the maximum period of supply is 3 months, the amount that a patient would be able to possess at one time would be 270 mg (assuming each month had 30 days).

8.4 Options for Presumption of Supply

Option 1: Status Quo

Option one is to set no presumption of supply. The default presumption of supply amount of 56 grams will apply.

This would approximately be 28,000 doses, assuming that the daily average clinical dose of etizolam was 2 mg.

Option 2: Proposed presumption of supply

Option two is to set a presumption for supply at **50 mg** for 25 doses of etizolam, assuming that the daily average clinical dose was 2 mg.

Alternatively, for the presumption of supply for 100 doses of etizolam, this would be **200 mg**, assuming that the daily average clinical dose was 2 mg.

9 FUTURE ACTIONS

If the Committee recommends that etizolam should be scheduled under the Misuse of Drugs Act 1975, the Secretariat will draft a letter from the Committee to the Minister of Health to progress the advice. The Secretariat may undertake targeted consultation with industry to ensure impact on legitimate uses of etizolam is reasonable and minimised.

If the status quo is recommended, no further action is required. The TCDO will remain in place until February 2023.

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