



**THE EXPERT ADVISORY COMMITTEE ON DRUGS (EACD)  
ADVICE TO THE MINISTER ON:**

**PEMOLINE**

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## **Executive Summary**

This paper considers the central nervous system stimulant pemoline - a substance that has been used to treat attention deficit disorder overseas. It has also been abused in some countries because of its amphetamine-like stimulant effects (Marnell 1999).

Pemoline is not controlled under the Misuse of Drugs Act 1975 (the Act). This assessment proposes that the Expert Advisory Committee on Drugs (EACD) considers recommending to the Minister of Health that pemoline be classified as a Third schedule (Class C) Part 5 controlled drug. Rationale for this view is provided in this paper.

Although the Ministry of Health is not aware of pemoline being used as a drug of abuse in New Zealand, the proposed classification for pemoline (ie. C5) will fulfil New Zealand's international obligations under the United Nations drug classification framework. Additionally, if pemoline becomes available in New Zealand in the future, appropriate domestic control will be in place.

## **Recommendations**

**After considering all of the information put to the Committee and the classification criteria in the Misuse of Drugs Act 1975, the EACD makes the following recommendations to the Associate Minister of Health:**

- (a) Pemoline should be classified in Part 5 of the Third Schedule of the Misuse of Drugs Act 1975 (ie, C5).**
- (b) This paper should be made publicly available (eg, posted on the National Drug Policy website [www.ndp.govt.nz](http://www.ndp.govt.nz)) as soon as practicable.**

## **Substances Identification**

Pemoline is a central nervous system stimulant that comes in a tablet form (Marnell 1999). It is not readily water-soluble and is usually administered orally as magnesium pemoline (WHO 1989). The name 'pemoline' is an International Non-proprietary Name (INN) - a form of international identification. Its chemical abstracts registry service (CAS) number is CAS 2152-34-3. Other identifications are: LA-956 and NSC-25159.

Pemoline can exist in two tautomeric forms (ie. a type of isomerism where the migration of a hydrogen atom results in two or more structures or tautomers). These are 2-amino-5-phenyl-2-oxazolin-4-one and 2-imino-5-phenyl-4-oxazolidinone. It is also called phenoxazole, phenylisohydantoin, and phenylpseudohydantoin. Pemoline has one chiral carbon atom, so two stereoisomeric forms and one racemate are possible (WHO 1989).

The Ministry of Health's Medsafe Unit advise that approval to market pemoline as a prescription medicine was granted in 1964, but the product was

withdrawn in 1989. Since then, Medsafe has not received any further applications for consent to market the drug as a prescription medicine.

### ***Similarity to Known Substances***

Although pemoline is structurally unrelated to amphetamines and methylphenidate, it possesses similar properties (Marnell 1999;+ WHO 1989). It has less rapid onset of action than amphetamine and its actions on the central nervous system do not peak until two to three hours after oral ingestion (WHO 1989). It has similar actions to dexamphetamine sulphate, but the effects of over-stimulation and sympathomimetic activity<sup>2</sup> are considered to be less with pemoline (Parfitt 1999).

### **Current and Proposed Classification**

Pemoline is not classified under the Act. However, it is classified as a prescription medicine in the First Schedule to the Medicines Regulations 1984.

It is recommended that pemoline be listed in Part 5 of the Third Schedule of the Act (ie, C5). This part of the schedule includes drugs that tend to be for medical uses and that have a moderate risk of abuse and dependence potential.

### **Rationale for Proposed Classification**

#### ***The Misuse of Drugs Amendment Act 2000***

The Act requires controlled drugs to be classified according to the risk of harm to individuals or society. Drugs posing a:

- **very high** risk of harm should be scheduled as 'Class A'
- **high** risk of harm should be scheduled as 'Class B'
- **moderate** risk of harm should be scheduled as 'Class C'.

To help assess the 'risk of harm' section 4B(2) of the Act also specifies a list of criteria that the EACD must consider when advising the Minister of Health on each drug. These criteria include:

- specific effects of the drug, including pharmacological, psychoactive, and toxicological
- likelihood or evidence of abuse, including prevalence of the drug, seizure trends, and potential appeal to vulnerable populations
- risk to public health
- therapeutic value of the drug
- potential for death upon use
- ability to create physical or psychological dependence
- international classification and experience of the drug in other jurisdictions

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<sup>2</sup> That is, producing effects that mimic stimulation of the sympathetic nervous system, eg. increased blood pressure and heart rate, and central effects such as fear, anxiety, tremor, restlessness, insomnia, confusion, and irritability.

- other matters considered relevant by the Minister
- potential presumption for supply and justification for this.

These criteria help guide the EACD decision as to what schedule (if any) is appropriate for the drug in question.

### ***Effects of the drug***

In summarising the pharmacokinetics of pemoline, Parfitt (1999) notes it is readily absorbed from the gastro-intestinal tract and about 50 percent is bound to plasma protein. The drug is partially metabolised in the liver and excreted in urine as a combination of its parent form and its less active metabolites.

Although its exact mechanism of action and its sites of action in the central nervous system have yet to be determined, pemoline does cause central nervous system and respiratory stimulation (Marnell 1999, WHO 1989). It can also increase motor activity and mental alertness, diminish fatigue, and produce a mild euphoria. The common side effects include: palpitations, excitability, nervousness, insomnia, tremors, pupil dilation, increased blood pressure and heart rate, nausea and vomiting (Marnell 1999). In large doses it can also produce hyperactivity, dyskinesia (impairment in the performance of voluntary movement), seizures, insomnia, hallucinations, and may aggravate psychosis (WHO 1989).

As found with many stimulants, drug induced anorexia may result in unhealthy weight reduction (Marnell 1999). Pemoline can also cause liver toxicity that may be fatal (Parfitt 1999; Marnell 1999).

Pemoline has similar actions to dexamphetamine although the effects of over-stimulation and sympathomimetic activity are considered to be less (Parfitt 1999).

### ***Likelihood or evidence of drug abuse***

Pemoline was withdrawn from commercial use as a prescription medicine in New Zealand in 1989. The Ministry of Health is not aware of pemoline currently being used as a drug of abuse in New Zealand. The New Zealand Customs Service advise that there was one mail intercept of pemoline in early 2001, but this was not thought to be linked to illicit use.<sup>5</sup>

The World Health Organization (“WHO”) Expert Committee on Drug Dependence first reviewed pemoline in 1985. The WHO concluded that while the drug had been in use in many countries, the data available at that time did not indicate it was likely to be associated with significant public health problems and therefore did not recommend it be scheduled under the United Nations drugs classification framework (WHO 1989).

However, the WHO reassessed its position four years later. Abuse was reported to the WHO by Belgium, the Federal Republic of Germany, Thailand, the United Kingdom, and Argentina. The United Kingdom reported that it was

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<sup>5</sup> Personal communication from new Zealand Customs Service to Ministry of Health dated 21 May 2001.

marketed “on the street” as “speed” and had been suspected in some cases of drugging of athletes and doping racehorses (WHO 1989).

The WHO noted that there had been reports of significant illicit trafficking in Europe, Africa, and South America (WHO 1989). For example, the number of seizures of pemoline in the United Kingdom increased from 12 (8064 dosage units) in 1985 to 17 (1,818,240 dosage units) in 1987 (WHO 1989). However, there was little information on what was happening to the trafficked pemoline. At that time, any estimates of the resulting public health and social problems remained inferences based on the quantities of the drug moving in international non-medical circles. However, the international traffic was at such a level that it was difficult to ignore (WHO 1989).

### ***Ability to create physical or psychological dependence***

In 1989 the WHO concluded that the dependence potential of the drug in humans had not been established and the evidence for or against it was not convincing (WHO 1989). The WHO noted:

“Pemoline is not self administered by rhesus monkeys and does not act as a reinforcer in these animals. Recent studies demonstrate that its reinforcing properties in humans are quite limited. It is typically not reinforcing or euphoriant at doses of up to 37.5 mg and is toxic and dysphoric at doses of 150 mg. At doses of 75 mg it has mild effects on the central nervous system, roughly equivalent to those of 15 mg of amphetamine. Its euphoric effects at this dose are significantly less than those observed with 30 mg of amphetamine. In contrast to the value placed on 15 mg of amphetamine, subjects did not view any dose as having any monetary value.”

However, more recently Parfitt (1999) noted a case of paranoid psychosis observed in a 38 year-old man taking 75 to 225 mg daily. The patient’s compulsive use, the development of tolerance, depressive withdrawal syndrome, and inability to abstain indicated dependence to pemoline. Marnell (1999) concludes that physical dependence to pemoline, due to its pharmacological action, does not occur, but psychological dependence can.

### ***Potential to cause death***

As with dexamphetamine, death can occur in acute overdose. Marnell (1999) notes that although overdoses can result in death due to convulsions and coma, it is unlikely except in extreme cases. In the United States pemoline has been associated with a small number of fatalities due to its toxicity to the liver (see Therapeutic Value below).

### ***Therapeutic value***

Pemoline has been used to manage attention deficit or hyperactivity disorders in children in the United States and in the United Kingdom (Parfitt 1999, Marnell 1999). However, in the late 1990s, the Committee on Safety of Medicines in the United Kingdom became aware of 33 reports of serious liver-related reactions in the United States, including 6 fatalities and the need for 2 liver transplants. A short time later, pemoline was subsequently withdrawn from the treatment of hyperactivity in the United Kingdom (Parfitt 1999). It has also been used to treat narcolepsy (Parfitt 1999).

## ***Risks to public health***

The 1989 WHO review reported that reliable evidence of extensive abuse or serious public health problems related to the non-medical use of pemoline was not evident. However, given the amount of pemoline reported to be moving in international channels at this time (which exceeded the amount required to meet any reasonable medical need), the WHO assumed that public health and social problems may have been developing and were likely to become increasingly obvious if current levels of non-medical use persisted.

Although pemoline does not appear to be a drug of abuse in New Zealand, it is reasonable to assume that if the drug became available its abuse potential could be similar to prescription amphetamines, which are abused for their euphoric effects. The use and distribution of such drugs has been controlled by legislation in many countries.

## **International classification and experience**

### ***New Zealand's international obligations under the United Nations Conventions<sup>5</sup>***

Scheduling of pemoline is required to align New Zealand control with the requirements of the United Nations Convention on Psychotropic Substances 1971 ("the 1971 Convention").

The WHO Expert Committee on Drug Dependence submitted an assessment of pemoline to the United Nations, along with a recommendation that the drug be classified under Schedule 4 of the 1971 Convention (WHO 1989).

Subsequently, the United Nations Commission on Narcotic Drugs voted to include pemoline in Schedule 4 of the 1971 Convention. New Zealand has ratified the 1971 Convention and is thus obligated to include pemoline within its domestic drug control regime. However, New Zealand has discretion as to how it classifies substances under its national legislation.

In 2000, the International Narcotic Control Board wrote to the Ministry of Health requesting that pemoline be classified under adequate domestic control (INCB 2000). The proposed classification for pemoline (ie. C5) will fulfil New Zealand's international obligations under the United Nations drug classification framework.

### ***Other countries' classification of pemoline***

In the United Kingdom pemoline is classified as a Class C controlled drug under the Misuse of Drugs Act 1971.

In the United States, it is classified in Schedule 4 of the federal Controlled Substances Act 1970.

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<sup>5</sup> For detail on the United Nations International drug classification framework please refer to the EACD paper entitled: *Comparing the United Nations International Drug Classification framework with New Zealand's Domestic Drug Classification Framework*.

## **Recommended Presumption for Supply and Justification**<sup>6</sup>

The EACD Secretariat does not recommend any presumption of supply for pemoline. However, this is an issue that the Committee may like to consider.

### ***Implications for harm minimisation principles***

There are no serious implications for harm minimisation. It is not thought that Pemoline is abused in New Zealand. It is therefore unlikely that moving Pemoline from the First Schedule of the Medicines Regulations 1984 to the Third Schedule (Class C) Part 5 of the Misuse of Drugs Act 1975 will either push it underground or cause users to divert to other potentially more harmful drugs.

### ***Other relevant information***

There is no other relevant information.

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<sup>6</sup> The Act contains provisions for setting a presumption for supply for controlled drugs (section 6(6)). This is a threshold where the simple possession of a specified amount of a drug is deemed to be for the purpose of supplying it to other people. Once the threshold is reached the onus is on the person to prove they were not in possession of the drug to supply other people. The EACD may decide to recommend a presumption for supply.

## **References**

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