

**ADVICE TO
THE EXPERT ADVISORY COMMITTEE ON DRUGS
ON:**

PSEUDOEPHEDRINE

JUNE 2009

**PREPARED BY
THE MINISTRY OF HEALTH**

PURPOSE

The Expert Advisory Committee on Drugs (EACD) has requested the secretariat prepare an advice paper for consideration by the EACD of the current classification of pseudoephedrine.

BACKGROUND

Since 1998 there have been a number of changes to the legal status of ephedrine (EPH) and pseudoephedrine (PSE) and controls on precursor substances.

In 1998, EPH and PSE were included in a new schedule for precursor substances (Schedule 4) in the Misuse of Drugs Act 1975 (MoDA). It was made an offence to supply, produce or manufacture any precursor substance knowing it would be used to commit an offence, such as producing or manufacturing a controlled drug.

In 2003, EPH and PSE were considered by EACD. In 2004, EPH was scheduled as a Class C5 controlled drug in the Misuse of Drugs Act 1975 (MoDA). PSE was scheduled as a Class C3 (partially exempted) controlled drug for certain preparations, Class C5 (partially exempted for sustained release preparations) and a Class C5 controlled drug for other preparations not covered by the restrictions for Class C3. Both drugs became subject to the licensing requirements of the Misuse of Drugs Regulations 1977.

EPH and PSE were considered to pose a risk to the public as principal ingredients in the manufacture of the Class A drug methamphetamine, rather than drugs in their own right. Their classification was intended to:

- Increased legislative control of the supply and use of these precursor substances;
- Give Customs wider powers to investigate importation syndicates, including the ability to conduct controlled deliveries;
- Allow for stronger penalties that would be a genuine deterrent to importation;
- Retain the availability of these substances as prescription and pharmacy-only medicines for legitimate use by the public.

In 2005, the Misuse of Drugs Amendment Act 2005 created new offences for knowingly importing or exporting precursor substances for unlawful use or without reasonable excuse. This further enhanced Customs powers to seize and detain precursor substances.

SUBSTANCE IDENTIFICATION / USES

The information in this section is based on sheets intended for the information of health professionals, found on the website of the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).

Pseudoephedrine Hydrochloride

Pseudoephedrine hydrochloride is an upper respiratory tract decongestant. It is widely available on the New Zealand market in a variety of approved products with variable dosages and preparations.

Ephedrine

Ephedrine, whilst similar in chemical structure to pseudoephedrine, is more potent and has different pharmaceutical applications. Ephedrine is solely a prescription-only

medicine with specific indications for use and thus less available for diversion into methamphetamine. On that basis, this paper will concentrate on pseudoephedrine.

Pharmacokinetics

Pseudoephedrine is readily absorbed from the gastrointestinal tract. It is largely excreted unchanged in the urine together with small amounts of its hepatic metabolite. It has a half-life of about 5-8 hours; elimination is enhanced and half-life reduced accordingly in acid urine. Small amounts are distributed into breast milk.

Pharmacodynamics / Mechanism of action

Pseudoephedrine has direct- and indirect- sympathomimetic activity and is an effective decongestant in the upper respiratory tract. It is a stereoisomer of ephedrine and has a similar action, but has been found to have less pressor (increase in blood pressure) activity and fewer central nervous system (CNS) effects.

Sympathomimetic agents are used as nasal decongestants to provide symptomatic relief. They act by causing vasoconstriction resulting in redistribution of local blood flow to reduce oedema of the nasal mucosa, thus improving ventilation, drainage and nasal stuffiness.

Indications

PSE preparations are indicated for the effective relief of runny nose, sinus and nasal congestion and sinus pain due to congestion. Some are intended to reduce the swelling and secretions in the nose and sinuses, allowing the patient to breathe more easily and relieving the pressure behind the nose and eyes, which is cause of sinus pain and headache.

Dosage & Administration

Most preparations recommend a dose of 60mg PSE three to four times daily with a maximum dose of 240mg per 24 hours. It is advised not to exceed the recommended dose and if symptoms do not improve within seven days a doctor should be consulted.

Contraindications

Pseudoephedrine is contraindicated for use in patients:

- with known hypersensitivity or idiosyncratic reaction to pseudoephedrine (or any of the other ingredients in the product);
- with severe hypertension or coronary artery disease;
- taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days.

Refer to 'Interactions' for additional information

Warnings and Precautions

Pseudoephedrine should be used with caution in patients with:

- hypertension
- hyperthyroidism
- diabetes mellitus
- coronary heart disease
- ischaemic heart disease
- glaucoma
- prostatic hypertrophy
- severe hepatic or renal dysfunction.

In December 2007, the Medicines Adverse Reactions Committee (MARC) reviewed the safety and efficacy of cough and cold medicines, including those containing pseudoephedrine, for use in children. The review concluded that there is:

- very limited evidence of efficacy of these products in children under two years of age
- an absence of evidence-based dosage advice for the use of cough and cold medicines in children aged less than two years
- evidence of harm in therapeutic use in this age group
- evidence of significant toxicity, including death, in overdose in this age group.

Medsafe has been working with suppliers to amend the product packaging to include warnings that these products must not be used in children under two years of age. Since 1 May 2009 all affected stock has carried this warning.

Refer to 'Interactions' for additional information.

Use in pregnancy

Pseudoephedrine and ephedrine have the Australian categorisation of Category B2 which is guidance for medicines use in pregnancy. B2 applies to drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data shows no evidence of an increased occurrence of foetal damage.

Pseudoephedrine should be used in pregnancy only if the potential benefits to the patient are weighed against the possible risk to the foetus.

Lactation

Pseudoephedrine is secreted in breast milk in small amounts. It has been estimated that 0.5% to 0.7% of a single dose of pseudoephedrine ingested by the mother will be excreted in the breast milk over 24 hours. Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

Effects on the ability to drive and use machines

The use of pseudoephedrine is likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

Adverse Reactions

Adverse effects include:

- cardiovascular stimulation - elevated blood pressure, tachycardia or arrhythmias
- central nervous system (CNS) stimulation - restlessness, insomnia, anxiety, tremors and (rarely) hallucinations
- skin rashes and urinary retention

Children and the elderly are more likely to experience adverse effects than other age groups.

Interactions

The following interactions with pseudoephedrine have been noted:

- Antidepressant medication e.g. tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) - may cause a serious increase in blood pressure or hypertensive crisis
- other sympathomimetic agents, such as decongestants, appetite suppressants and amphetamine-like psychostimulants - may cause an increase in blood pressure, as well as produce additive effects and increased toxicity
- methyl dopa and β -blockers - may cause an increase in blood pressure
- urinary acidifiers enhance elimination of pseudoephedrine
- urinary alkalinisers decrease elimination of pseudoephedrine

Overdosage

Symptoms associated with pseudoephedrine overdose may include restlessness, excitement, nervousness, nausea, vomiting, abdominal pain, ataxia, hallucinations, convulsions and tachycardia.

In the event of overdose, medication should be discontinued and medical help sought immediately.

SIMILARITY TO KNOWN SUBSTANCES

The information in this and subsequent sections is based on a paper for Ministers by an Inter-Agency Committee on Drugs (IACD) working group on options to reduce the diversion of precursor chemicals from pharmacies for the manufacture of methamphetamine. Decisions on the paper are yet to be made. More information will be provided to the EACD if required.

Phenylephrine

In recent years the health sector has encouraged the development and use of non-PSE based remedies such as phenylephrine to provide alternatives to PSE and reduce the risk of being targeted by individuals wishing to obtain PSE to produce methamphetamine.

Market shift from pseudoephedrine

Since 2005, there have been no new applications to market any products containing PSE either singly or in combination. Medsafe's database contains 134 names of products for which an application has been made, or has been approved. As of August 2008, only 43 of these products continue to have consent, with the remaining 91 products being either withdrawn or discontinued. A number of discontinuations occurred as companies reformulated their cough and cold products to include phenylephrine (from 2002 onwards).

Commercially sensitive information shows that between 2000 and 2007 the domestic EPH / PSE retail market halved, with progressive reductions each year. It is believed that this has occurred due to a combination of the shift to alternatives (mainly phenylephrine) as well as pharmacy awareness, voluntary control measures to prevent sales for illegitimate purposes and the removal of PSE product from some pharmacies.

Medsafe's database contains 83 entries for products including phenylephrine. As of August 2008, a total of 63 of these products either have consent to market or their application for approval is pending. Most of the 63 products in this group submitted applications after 2005.

The products containing phenylephrine¹ approved or pending include a number of products from each of the major cough and cold products including the Sudafed, Vicks, Robitussin, Demazin, Coldrex, Benadryl, Panadol and Lemsip brand names. There is considerable overlap between the two substances in the consumer market with companies maintaining consent for products within the same umbrella brand (e.g. Sudafed), some of which contain PSE and others which contain phenylephrine. The range of phenylephrine brand name products available is broad enough that consideration can be given to differentiating between the products through different levels of access and control, such as by reclassifying PSE.

United Kingdom (UK) proposals

In 2007, UK authorities announced proposals to restrict the availability of medicines containing EPH / PSE by changing their legal status from pharmacy to prescription only medicines. A consultation process began with a view to reclassification but no action is known to have been taken at the time of preparing this report. The UK is also supporting the development of alternative products and reports that PSE is not necessarily an essential medicine for treating coughs and colds and the evidence supporting its effectiveness is limited.

In the UK, both PSE and phenylephrine products are known to produce very similar effects and side effects. There is some evidence that PSE is more likely to produce CNS effects than phenylephrine, and there is pharmacodynamic evidence that PSE binds more strongly to the receptors that decrease blood flow to mucous surfaces and that the decongestant effect lasts longer than phenylephrine.

However, UK reviews to date have found that:

- there was little in the way of quality clinical trial evidence of actual benefit associated with either of these products in the treatment of coughs and colds
- the pharmacy professions who stated that phenylephrine was less effective had not reviewed or considered data on the effects of repeat dosing with phenylephrine

¹ Phenylephrine is often referred to as "PE", including on packaging – e.g. "Sudafed PE"

- the claim that consumers preferred PSE may have been essentially anecdotal evidence.
- Patients did not distinguish between PSE or phenylephrine based products due to the umbrella branding of products containing either substance. This suggests that changes to phenylephrine products would be relatively straightforward for most patients.

Phenylephrine cannot be converted by simple chemical processes to methamphetamine.

CURRENT CLASSIFICATION

EPH is a Schedule 3, Part 5 (Class C5) controlled drug. PSE is both a Schedule 3, Part 3 (Class C3) and Schedule 3, Part 5 (Class C5) controlled drug, depending on the preparation.

As EPH and PSE are controlled drugs, they are subject to controls under MoDA. As a Class C5 drug, EPH is a prescription medicine. Class C5 (in package quantities greater than 1.8g) preparations of PSE are prescription medicines. Prescription medicines may be supplied only on the prescription of a medical or dental practitioner, midwife or veterinary surgeon.

Another listing of Class C5 allows the sale of preparations of PSE in modified or sustained release formulations that deliver no more than 240mg of PSE in a 24-hour period. These preparations are defined as 'partially exempted'.

Class C3 preparations of PSE are 'partially exempted' pharmacy-only medicines if they are cough/cold/flu or decongestant preparations where the package in which the preparation is sold or supplied contains not more than 1.8 grams of PSE. Pharmacy-only medicines may only be sold in a community or hospital pharmacy, or a shop in an isolated area that is licensed to sell that particular medicine. The sale may be made by any salesperson.

The Class C3 category for PSE largely covers common cough and cold decongestants; while the Class C5 category controls higher PSE-bearing medications.

CLASSIFICATION OPTIONS

The secretariat has identified the following options for consideration by EACD. All of the options may reduce the availability for domestic PSE to be diverted for the purposes of methamphetamine production:

1. That the MoDA schedules are amended so that all preparations of PSE are classified as Class C5 controlled drugs and are re-defined as available only by prescription; **or**
2. That the status of PSE-bearing medicines currently scheduled as Class C3 (and C5 partially exempted formulation) controlled drugs is amended from being pharmacy only medicines to Restricted Medicines (pharmacist only medicines); **or**
3. That current legislative controls remain in place, but that further development and use of alternative non-PSE based remedies such as phenylephrine is encouraged to replace PSE in the market.

These options may also require consultation with the Medicines Classification Committee (MCC).

Discussion

1. Prescription only

Reclassification of PSE from pharmacy to prescription to medicine may be justified on the grounds of reducing harms to the public health. It will reduce the availability from pharmacies and thus opportunities for diversion. An increase in doctor visits that may result may ensure medication is appropriately prescribed and more serious health indicators identified.

This option would make it more difficult for consumers to obtain PSE products. A further strength of making PSE a prescription only medicine is that the details that are required from the patient provide an in-built identity check. This option may not completely eliminate diversion as there would be a certain amount of “doctor shopping” that is visiting multiple doctors, or forging or manipulating prescriptions.

There may be instances when pharmacists may not feel comfortable with a prescription for larger amounts of PSE. In these circumstances pharmacists are expected to contact the prescribing doctor (usually by telephone) to discuss refusal of the prescription. There have been occasions where doctors have been persuaded or have been coerced or forced to prescribe drugs for misuse. It is not known how requiring a prescription for PSE would impact on this problem.

A significant issue that would need to be addressed before supporting this approach would be the perception that unnecessary costs are being borne by the user to access prescriptions through GP visits for what could be considered minor health issues.

2. Restricted Medicine

PSE could be made a Restricted Medicine, also known as pharmacist only medicine. This would limit any sales of PSE-bearing products to be made by a registered pharmacist only.

The Restricted Medicine status carries special legislative responsibilities controlling the sale, record-keeping, storage and advertising of the medicines scheduled in this category in the Medicines Regulations 1984. The sale must be made by a pharmacist in a pharmacy or hospital and the records of each sale must contain the following information:

- name and address of the purchaser,
- name of the pharmacist,
- date of the transaction; and
- name and quantity of the medicine sold.

The storage of the medicine within the pharmacy must be in a place to which young children or unauthorised persons do not have ready access, i.e. it is not available for public self-selection. In addition, advertising of restricted medicines must not mislead customers regarding the classification and the requirements for the sale.

The majority of pharmacies already request identification before making a sale of PSE and most sales are currently made or supervised by pharmacists. Therefore a reclassification to a pharmacist only medicine would not represent a significant change to current practice.

3. Market shift to phenylephrine

The market for cough and cold medications has shifted over the last decade. Medsafe has actively facilitated the entry of products substituting phenylephrine for PSE. (See Similarity to Known Substances)

Commercially sensitive data indicates that retail sales of PSE-based products in New Zealand pharmacies halved between 2000 and 2007. This reduction may be linked to a number of factors:

- success of some existing anti-diversion measures, primarily existing pharmacy-to-Police reporting mechanisms;
- increased illegal importation of PSE;
- legislated limits in dosage and package sizes;
- pharmacies being less willing to supply; and
- significantly increased promotion and availability of phenylephrine products (e.g., Sudafed PE) as alternatives to PSE.

The on-going trend towards replacing PSE with phenylephrine in the market will reduce stock levels of PSE in pharmacies and thus its availability for diversion. The replacement of PSE with phenylephrine and other alternatives could be further encouraged, with eventual elimination of PSE products as the end goal.

CRITERIA FOR CLASSIFICATION / RECLASSIFICATION

Section 4B(2) of the MoDA sets out the matters which the Minister of Health must have regard to, and to which the EACD must give advice on, when considering a particular drug. Information on each criterion is required.

LIKELIHOOD OR EVIDENCE OF ABUSE

New Zealand prevalence data

Medsafe has no data on the misuse of PSE. However, PSE is a major ingredient in the manufacture of the Class A controlled drug methamphetamine in New Zealand. Survey data shows that methamphetamine use in New Zealand is high by international standards, but is declining. Last year use of amphetamines, including methamphetamine, among 15 to 45 year olds reached a high of 5.0 % in 2001 and reduced to 4.0 % in 2003 and 3.4 % in 2006. Provisional data from the Ministry's *Alcohol and Drug Use 2007* national survey and the pending 2008 Illicit Drug Monitoring System (IDMS) survey suggest this downward trend is continuing, with last year use among 13 to 65 year olds likely to now be at between 2 and 3 percent. The 2008 IDMS also indicates frequent methamphetamine users are finding the drug more difficult to obtain than in previous years.

However, IDMS data from 2007 and 2008 and anecdotal information from treatment providers suggests an increase and entrenchment of use by regular users and some increase in the numbers of those seeking help. Qualitative data from the 2007 IDMS also indicate methamphetamine users experienced more health, financial and police / legal problems in relation to their use than in the previous two years of the survey.

Current pharmacy controls

In general, the current classifications provide pharmacies with a significant level of control over, and responsibility for the sale and supply of PSE-bearing products. Voluntary measures have been put in place by most pharmacies to reduce the diversion of PSE. These include:

- a limit on sales, e.g. a one package limit
- requesting customer identification as a condition of sale and recording sales

- stocking products behind the counter
- a requirement that the pharmacist only is involved in sales of the product.

In some areas groups of pharmacists have ceased to stock products containing PSE altogether. Other measures include cooperation between pharmacies and with Police in some districts. Overall, it is considered that pharmacies manage the sale of PSE well. However, there are no controls to enable pharmacies to be aware of previous purchases made by a customer from other sources and there is no nationally agreed protocol for reporting PSE sales to Police.

As a precursor to methamphetamine

PSE is the main ingredient used to manufacture methamphetamine in New Zealand. While the majority of PSE is sourced via illegal importation, Police estimates one-third of all clandestine laboratories (clan labs) detected contain PSE that has been obtained from pharmacies. It is estimated that the PSE located at the remaining two-thirds of clan labs is either unidentifiable or illegally imported. Police intelligence indicates that domestically sourced PSE is more commonly found in lower scale clan labs.

In addition to PSE diversion from pharmacies and illegal importation of PSE products there is also concern about the diversion of common domestic chemical agents (such as acetone, toluene and hydrochloric acid) that are used in the manufacturing process.

New Zealand experienced a large increase in methamphetamine production during most of the past decade. Since 1999, the number of clan labs dismantled by Police increased from 5 to a peak of 211 in 2006. There were 190 clan labs dismantled in 2007 and 133 in 2008. The projected total for 2009 also appears to be reduced. It is not clear whether recent reductions reflect a stabilisation of domestic manufacturing capacity or the limits of Police response capability.

Seizures

NZ Customs reports that seizures of illegally imported PSE amounted to the equivalent of 2.2 million tablets in 2006; 1.8 million in 2007; and more than 3.3 million in 2008. The majority of seized product is in various forms of "ContacNT" and is sourced from one factory in China. The NDIB estimates that the equivalent of over 10 million tablets is illegally imported annually - which represents over 900kg of pure PSE. The end destination of the bulk of imported ContacNT is not known. The majority of imported product contains a higher PSE content than that sourced domestically.

SPECIFIC EFFECTS OF THE DRUG

See Substances Identification / Uses section for specific effects of PSE as a medicine.

RISKS TO PUBLIC HEALTH

The diversion of PSE to the manufacture of methamphetamine represents a significant risk to public health.

The primary public health risk specific to methamphetamine is exposure to substances and chemical processes used to manufacture methamphetamine. This includes the risk of explosion, chemical burns and poisoning.

Other risks include the transmission of communicable diseases such as HIV / AIDS and Hepatitis B and C (injecting drug users), the impact on the ability to drive (e.g. increased risk taking, post-use fatigue or withdrawal), and possible prenatal complications, increase rates of premature delivery, altered neonatal behaviour patterns and developmental disorders.

THERAPEUTIC VALUE

See Substances Identification / Uses and Similarity to Known Substances sections for therapeutic value of PSE.

POTENTIAL TO CAUSE DEATH

PSE does not represent a risk of death of itself.

In New Zealand, there are no known deaths specifically associated with the use of methamphetamine. New Zealand does not have a system in place to provide up-to-date drug related mortality data with the ability to specifically identify methamphetamine. In Australia, there are approximately 50 deaths per year directly attributed to stimulant use (including methamphetamine).

ABILITY TO CREATE PHYSICAL OR PSYCHOLOGICAL DEPENDENCE

PSE has a very low ability to create physical dependence, however it is used extensively by some people for the alleviation of cough and cold symptoms.

Methamphetamine is a highly addictive stimulant. The potential for dependence is subject to dosage and route of administration, due to its effect on the dopamine neurotransmitter. Research indicates that methamphetamine can have a more rapid progression from 'recreational' to problematic use than cocaine and the duration of the 'high' produced by methamphetamine is up to twenty times longer than that produced by cocaine.

INTERNATIONAL CLASSIFICATION AND EXPERIENCE IN OTHER JURISDICTIONS

United Nations Conventions Scheduling

Precursor chemicals used for illicit drug manufacture are covered by the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (the Vienna Convention), to which New Zealand is a party. EPH and PSE are listed in Table I of the Vienna Convention, as they are considered 'immediate chemicals'. Other 'essential chemicals' such as reagents and solvents including acetone, toluene and hydrochloric acid are listed in Table II.

Monitoring and reporting on the licit trade of substances in both Tables I and II is an ongoing requirement of the Vienna Convention, as is the reporting of seizures of these substances. It is also a requirement on parties to allow for criminal offences where these substances are used, or intended for use, in the illicit manufacture of drugs.

Other Jurisdictions

A number of other jurisdictions have restricted the availability of EPH and PSE in various ways, particularly those who are experiencing problems with methamphetamine manufacture and use. In the Commonwealth of Australia's Standard for the Uniform Scheduling of Drugs and Poisons, PSE is listed as a Schedule 2 Pharmacy Medicine; Schedule 3 Pharmacist Only Medicine and Schedule 4 Prescription Only Medicine, depending on the preparation.

The US state of Oregon, and Mexico have recently made PSE a prescription only medicine. As noted above, the UK is also considering reclassification of PSE to a prescription only medicine.

The Netherlands withdrew PSE from the market in 1989 because of concern about the cardiac safety of the drug.