Advisory Committee for Medicines Scheduling
Meeting July 2015

Response by Penington Institute to invitation for public submission on application to amend the scheduling of naloxone to include single use prefilled syringe preparations for injection containing 400 micrograms/mL of naloxone or less in Schedule 3

Closing date for submission – 7 May 2015

Contact person: John Ryan
Position: Chief Executive Officer
Contact details:
j.ryan@penington.org.au
03 9650 0699

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1. PART 1 – SUMMARY OF SUBMISSION

1.1 PROPOSED SCHEDULING / RESCHEDULING TO THE *POISONS STANDARD*

Penington Institute refers to the invitation for public comment on the application made to amend the scheduling of naloxone to include single use prefilled syringe preparations for injection containing 400 micrograms/mL of naloxone or less in Schedule 3

Penington Institute agrees with the proposed rescheduling submitted for public consultation by July 2015, and provides this submission in support of the existing rescheduling application. To ensure that adequate detail has been included in this submission, Penington Institute has used the structure, and fulfilled the requirements of, a rescheduling application.

1.2 SUGGESTED SCHEDULING OR OTHER WORDING

(a) **Schedule 3 – proposed new entry**

NALOXONE in single-use preparations for prefilled injection containing 400 micrograms/mL of naloxone or less.

(b) **Schedule 4 – modified entry**

NALOXONE **except** when included in Schedule 3.

1.3 SUBSTANCE SUMMARY

Naloxone hydrochloride (also referred to simply as ‘naloxone’, and known by the brand name Narcan®) is a type of medication called an “opioid antagonist”. Naloxone (CAS Number 465-65-6) is a life-saving medicine that temporarily reverses the life-threatening depression of the central nervous and respiratory systems that occurs in overdose.

1.4 OVERVIEW

Naloxone hydrochloride is an opioid antagonist that completely or partially reverses the effects of natural and synthetic opioids such as codeine, heroin, methadone, morphine and oxycodone. It is non-addictive and safe, primarily because it does little else but counter the depressant effects of opiates. Since the 1970s it has been used by paramedics and emergency room physicians to reverse the effects of opioids, including in people suffering a life threatening overdose. Thousands of lives are saved and severe brain injuries avoided each year by Australian paramedics who carry it with them as part of standard practice.

As in other parts of the world, there are now some small-scale programs in Australia where potential overdose witnesses (such as opioid injectors) are provided access to naloxone through what are known, in some areas, as ‘take home naloxone’ programs. These programs are conducted, for example, through health services and patients/clients receive a script which can then be claimed against the PBS. Although

Australian programs are quite limited in scale to date, indications are they are successful [1].

A limited rescheduling of naloxone from a Schedule 4 Prescription Only Medicine to a Schedule 3 Pharmacist Only Medicine would assist in providing much needed access to naloxone in the wider community. Pharmacists are highly educated medication specialists who are easily accessible to the public. A rescheduling would allow pharmacists to supply naloxone without prescription, which would assist reduce the number of fatal opioid overdoses in Australia.

2. PART 2 – BODY OF SUBMISSION

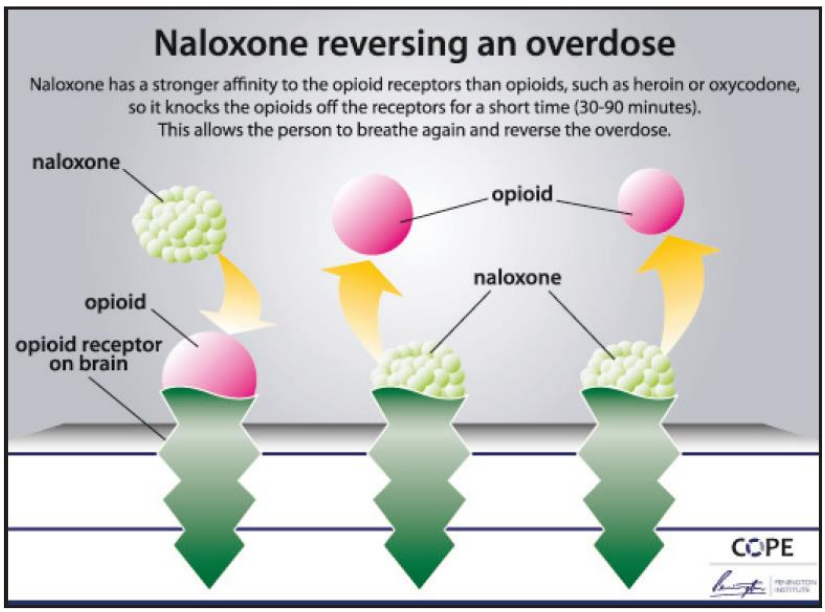
2.1 BACKGROUND

Opioids (such as oxycodone, morphine, heroin, codeine and methadone) are central nervous system depressants, which, in the case of overdose, gradually suppress respiration. Without intervention, opioid overdose can lead to permanent brain injury or death [2, 3].

Australia is in the midst of a prolonged problem of accidental and preventable deaths associated with overdose of licit and illicit opioids [4-6].

Naloxone hydrochloride is an opioid antagonist. It works by knocking the opioids off the body's receptors for a short time (around 30 to 90 minutes), as indicated in the diagram below. This is because naloxone has a stronger affinity to the opioid receptors than many opioids [2].

In Australia, naloxone is currently listed as a Schedule 4 Prescription Only Medicine.



Source: Adapted diagram from *Guide To Developing and Managing Overdose Prevention and Take-Home Naloxone Projects* http://harmreduction.org/our-work/overdose-prevention/

Figure 1: *The operation of naloxone*

2.2 CRITERIA TO BE SATISFIED FOR APPLICATION FOR RESCHEDULING (CHANGE TO PART 4 OF THE *POISONS STANDARD*)

(a) **Risks and benefits associated with the use of naloxone**

It is Penington Institute's experience that in Australia, the naloxone formulation in question has been under-prescribed. General practitioners have been be reluctant to prescribe naloxone to people at risk of overdosing, or to family members of those at risk. Naloxone has historically only been used by medical personnel (eg: qualified hospital staff or paramedics) to reverse the effects of opioid overdose.

In many circumstances, emergency medical help is not sought in response to overdose due to a fear of police involvement when illegal substances are being used, or because witnesses do not recognise overdose symptoms as life-threatening [7]. In rural settings, emergency help may not arrive in a timely manner to treat an overdose [8].

While not all opioid overdoses are life-threatening, a significant number of lives could be saved each year if laypeople were able to provide naloxone to overdosing persons who may otherwise not have received medical intervention in time [9]. Naloxone can be administered by minimally trained laypeople without causing any harmful effects [10, 11].

Additionally, rescue breathing and timely administration of naloxone by a witness of an overdosing incident may help reduce some of the morbidities associated with non-fatal overdose, including brain damage [9]. This is a similar scenario to laypeople administering adrenaline to anaphylaxis sufferers using an EpiPen. The wide accessibility of EpiPens through pharmacies means that potential witnesses of anaphylaxis, such as the family and friends of those with severe allergies, are able to instantly respond to life-threatening situations and save the lives of their loved ones.

International evidence also indicates that providing naloxone, with appropriate training, to opioid users and to potential overdose witnesses such as their family and friends, can result in successful overdose reversal in a safe and effective manner. For example, a US comparative study indicated that providing naloxone hydrochloride and training to drug users, their families and friends involved a reported 10,171 overdose reversals [12]. In December 2011, Australia's first overdose management program was launched in the ACT, providing naloxone on prescription to people at risk of overdose. Independent evaluators released an interim findings report on 13 February 2014, assessing the implementation fidelity and participants' experience of the program [13]. The findings revealed that the 140 program participants evaluated displayed a higher knowledge of overdose identification and response after the completion of the training compared to before. The report also revealed that they were able to administer naloxone in a non-medical setting which resulted in 23 successfully reported overdose reversals. The evaluation concluded that the ACT take-home naloxone program was overwhelmingly positive.

Programs that train potential overdose witnesses to recognise overdose signs, respond appropriately and be provided prescriptions for naloxone are now also operating in Victoria, New South Wales, South Australia, Western Australia and Queensland [14]. Under these programs, people at risk of overdose are being provided scripts and are

dispensed naloxone by pharmacists. With the exception of Victoria, these are still regarded as limited in scope, and also scale.

There are very few risks associated with naloxone use, including that of overdose. A very small number of people have hypersensitivity to naloxone. The sudden return to consciousness of an overdosing person may sometimes be associated with tremor and hyperventilation [15]. If a large dose is given to a person with opioids in their system, they may experience symptoms of opioid withdrawal. However, this is based on existing dependence on opioids. Naloxone cannot cause physical or psychological dependence [15].

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

Naloxone is an opioid antagonist able to reverse life-threatening central nervous and respiratory depression caused by opioid overdose [2].

Naloxone, as a Schedule 4 medicine, may be safely and legally administered by a lay person, but only to the person named on the prescription. The current scheduling does not fully utilise opportunities for more lives to be saved.

If there is a provision for the single use injection form of naloxone to be available as an S3 drug the limitation that the drug be only used for named persons is removed. There are circumstances, for example in drug treatment facilities, where the identity of a specific overdose victim may not be known before the event. In these cases naloxone could be legally used by a lay person if it had been obtained as a Schedule 3 drug. In this circumstance, the control point would be with the pharmacist who would be in a position to assess whether the intended use was safe and appropriate.

The below graph shows the number of prescriptions for the UCB minijet which have been processed by the Pharmaceutical Benefits Scheme (PBS) since January 2013. It should be noted that some of the emerging (pilot) take-home naloxone programs have been paying for patients' scripts to be dispensed. Prescriptions paid for through such a program would not be taken into account for the below graph. These low numbers reveal that there is an urgent need to promote naloxone availability nationally so that the full public health benefit can be realised.

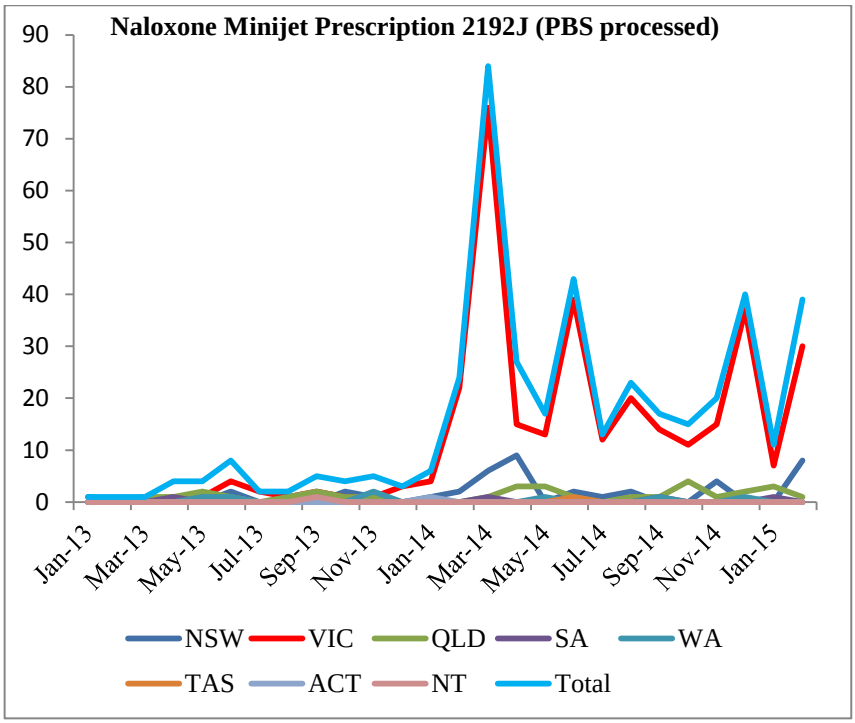


Figure 2: *Naloxone UCB minijet prescriptions processed by the PBS.*

Under the proposal before the TGA, pharmacists would only be able to dispense single-use pre-filled syringes. Penington Institute supports that proposal, on the condition that this formulation remains listed on the Pharmaceutical Benefits Scheme.

(c) **Toxicity and safety of naloxone**

Naloxone is a safe and effective drug that only works if a person has opioids in their system and has no effect if opioids are absent. People cannot develop a dependency on naloxone. It can be injected into a muscle, vein or under the skin and has a temporary effect that wears off in 30-90 minutes [2]. A study of nine healthy volunteers found that five minutes after the injection of 400µg of naloxone hydrochloride 97% of the dosage was no longer found in the blood serum [16]. This indicates the short duration of action of the drug.

The risk profile of naloxone is well defined. The safety and risks of naloxone have been previously considered by the TGA and are outlined in Product Information sheets [17]. The World Health Organisation recognises that the efficacy and safety profile of naloxone makes it ideal for treating overdose in the community setting [18].

Naloxone provision to potential witnesses of overdose is currently occurring in Canada, England, Germany, Georgia, Russia, Scotland, Spain, Norway, Wales, Afghanistan, China, Kazakhstan, Tajikistan, the United States and Vietnam [9, 19-21]. It has been available over-the-counter in Italy since the 1980s without any reported negative consequences [22].

(d) **Dosage, formulation, labelling, packaging and presentation of naloxone**

Naloxone is supplied as an intra-muscular injection under the Pharmaceutical Benefits Scheme (PBS) as naloxone (prescriber code 2192J). It is available in a minijet 400µg/1mL solution which is ideal for intramuscular injections.

Naloxone has a shelf life of approximately two years. An expiry date is printed on the minijet and refers to the last day of the month indicated. The manufacturer of the minijet recommends keeping naloxone in the box until use, out of direct sunlight.

Manufacturers recommend that naloxone be stored below 25 degrees Celsius. However, it is a very sturdy drug and remains effective when stored at temperatures above 25 degrees. It is unlikely that it will degrade to a non-effective level if left in an unrefrigerated or un-air-conditioned space – such as a cupboard or drawer – during summer.

(e) **Potential for misuse/abuse of naloxone**

There is no use for naloxone other than for the reversal of the effects of opioids. Therefore, naloxone "has no abuse liability or potential for misuse" [2]. Due to this, naloxone has no currency or value on the "black market".

The United Kingdom's Advisory Council on the Misuse of Drugs (ACMD) concluded the following with regards side-effects and misuse potential:

> *"Naloxone brings on temporary withdrawal symptoms in an individual who has opioids in their system, but on people who do not have opioids in their system, there are no such withdrawal effects. Naloxone has no intoxicating effects or dependence-forming potential.*
>
> *"Side-effects are rarely reported. When side-effects have occurred, they were mostly associated with pre-existing medical conditions. (Bryson, 1996; Sporer et al., 2007). They are also associated with significantly higher dose levels than those used in peer overdose interventions" [23].*

(f) **Other factors relevant to the scheduling of naloxone**

According to the National Coronial Information System (NCIS), the majority of national opioid related deaths across a five year period (2007-2011) were deemed unintentional (71.2% of 4102 deaths) [4]. Overdose claimed the lives of 384 Victorians in 2014 alone [24]. This figure is much greater than the road toll of 249 Victorians in the same year [25].

The Salvation Army's Access Health in Melbourne has been arranging for potential overdose witness to be trained in overdose prevention and response. The program also arranges naloxone prescriptions and dispensing. Several overdose reversals have been achieved by participants. The experience of one participant, who was prescribed naloxone after receiving training at Access Health, highlights the benefit that increased access to naloxone is already providing, and will continue to provide if access is further expanded:

> "I've never overdosed in my life. I don't know why. I've brought back 14 people. I've had 14 people OD in my room and I've had to [use] CPR

> and everything. I used the pens [naloxone minijet] about three weeks ago. There was a chick that was nodding off in my front yard. I could still hear her breathing, but it just got slowly and slowly and eventually her face turned purple so [I injected her]. One pen [minijet] didn't work so I used the other one straight through the clothing"[1] .

2.3 CONCLUSION

Overdose, including from opioids, is a leading cause of accidental death in Australia. External administration of naloxone hydrochloride is able to prevent or substantially reduce the negative health consequences of an opioid overdose. Naloxone is a safe drug which is safe to be administered to people. It only has effect when there are opioids present in the body. Therefore, it poses no potential for abuse. Naloxone is simple to administer by witnesses of an overdose, with limited instruction.

At present, naloxone is only available to people at risk of overdose, through a prescription. While it is encouraging that there are now some take-home naloxone programs in Australia, the coverage and scale of these programs is limited. There is a need to increase access to this lifesaving drug, as is occurring in a number of nations such as the United States.

It is clear that naloxone remains under-prescribed and, therefore, is not currently being used to its full potential as an opioid antagonist in overdose situations. Scheduling the single-use pre-filled syringe 400µg/1mL as a Pharmacist Only medication, while maintaining it on the PBS, will increase the options available to community members wishing to receive naloxone.

Rescheduling single use naloxone to Schedule 3 of the *Poisons Standard* would improve community members' access to this drug and therefore save lives.

PART 3 – SUPPORTING DATA

Annexure 1: UK Government, The Advisory Council on the Misuse of Drugs, 'Consideration of naloxone' (8 May 2012).

3. PART 4 – BIBLIOGRAPHY – SEE ATTACHED COPIES

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Coroners Court of Victoria, Asia Pacific Coroners Society conference 2014 http://www.asiapacificcoroners.org/assets/2014Presentations/0915Dwyer.pdf (**Attachment 4**)

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Harm Reduction Coalition; Guide to developing and managing overdose prevention and take-home naloxone projects http://harmreduction.org/wp-content/uploads/2012/11/od-manual-final-links.pdf (**Attachment 6**)

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