



Australian Government

Department of Health

Therapeutic Goods Administration

Delegate Information Packs for a delegate of the Secretary to the Department of Health - DELEGATE APPROVED 4.4.18

Advisory Committee on Medicines Scheduling (ACMS) 24 – June 2018

Delegate information pack (DIP) for:

- Medicines scheduling proposals received for the June 2018 meeting cycle.

Delegations

As an EL2 in the Scientific Evaluation Branch or a Medical Officer Class 5 in the Pharmacovigilance and Special Access Branch, you have powers delegated by the Secretary of the Department of Health under subsections 52D(2) and 52E of the *Therapeutic Goods Act 1989* (the Act) to amend or replace the Poisons Standard [52D(2)] and in doing so, seek advice from any person or committee that the Secretary considers appropriate [52E(4)].

Seeking advice on proposed scheduling amendments

According to subsection 52E(4) of the *Therapeutic Goods Act 1989* (the Act), in exercising a power under subsection 52D(2), the Secretary may seek advice from any person or any committee that the Secretary considers appropriate (whether or not the committee is established under the Act or the *Therapeutic Goods Regulations 1990*). This includes an evaluator, the Advisory Committee on Medicines Scheduling (ACMS) and/or the Advisory Committee on Chemicals Scheduling (ACCS). Subsection 52E(3) of the Act also sets out that, where the Secretary decides to seek the advice of the ACMS and/or the ACCS, the Secretary must have regard to that advice.

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Timeframes

Evaluations

If you decide an evaluation is required for an application, the evaluator will require at least 6 weeks to complete an evaluation (see table below). The secretariat would appreciate your decision to evaluate an application by **29 March 2018**.

Timeframes for an evaluation

Application to evaluator	2 April 2018
Evaluation report due to Secretariat and to applicant	30 April 2018
Comments due to Secretariat and to evaluator	14 May 2018
Rejoinder due to Secretariat	28 May 2018

ACCS advice

If you decide these matters require ACCS or Joint ACCS-ACMS advice, then the public notice of proposed amendments must be published on the TGA website on 12 April 2018. Your decision regarding referral to ACCS or Joint ACCS-ACMS for advice and your confirmation of the details to be included in the public notices is required by **29 March 2018**.

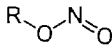
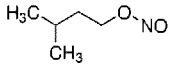
Delegate-only decision

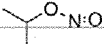
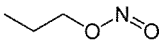
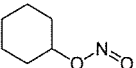
1. If you decide that an application *does not require ACCS or Joint ACCS-ACMS advice* and that a delegate-only decision is appropriate and that the decision is the same as the applicant's proposal, then the final decision and reasons for the decision will be published on the TGA website with the March 2018 cycle final decisions, on 23 August 2018. Your final decision is therefore required by **26 July 2018**; or
2. If you decide that an application *does not require ACCS or Joint ACCS-ACMS advice* and that a delegate-only decision is appropriate but that it is different from the applicant's proposal, then the decision will be an interim decision and will be published on the TGA website with the March 2018 cycle interim decisions on 7 June 2018. The secretariat will also notify the applicant in writing of your interim decision and provide the applicant at least 20 working days to make a written submission in response to your decision. Delegate-only decisions that are different from the applicant's proposal are therefore required by **26 April 2018**.

Note – pages 4 to 51 inclusive do not relate to alkyl nitrites and have been redacted as irrelevant under s 22(1) of the FOI Act

7. Alkyl nitrites

Summary table of delegate-initiated proposal

Substance	Properties
Examples of volatile alkyl nitrites not already listed in the SUSMP	Chemical structure:  Molecular formula: R-NO ₂
IUPAC and/or common and/or other names: isopentyl nitrite (nitrous acid, 3-methylbutyl ester, isoamyl nitrite)	CAS number: 110-46-3 Chemical structure:  Molecular formula: (CH ₃) ₂ CHCH ₂ CH ₂ ONO Molecular weight: 117.15
IUPAC and/or common and/or other names: 2-propyl nitrite (IUPAC)	CAS number: 541-42-4

synonyms: isopropyl nitrite, isopropyl alcohol nitrite, nitrous acid, isopropyl ester, 1-methylethyl nitrite, 2-propyl nitrite	<p>Chemical structure:</p>  <p>Molecular formula: C₃H₇NO₂</p> <p>Molecular weight: 89.09</p>
IUPAC and/or common and/or other names: N-propyl nitrite, Propyl nitrite; Propanol nitrite; Nitrous acid, propyl ester; N-Propyl-nitrite	<p>CAS number: 543-67-9</p> <p>Chemical structure:</p>  <p>Molecular formula: C₃H₇NO₂</p> <p>Molecular weight: 89.09</p>
IUPAC and/or common and/or other names: cyclohexyl nitrite (IUPAC) (nitrous acid, cyclohexyl ester; N-cyclohexyl nitrite; cyclohexyl alcohol nitrite; C-hexyl nitrite; O-nitrosocyclohexanol)	<p>CAS number: 5156-40-1</p> <p>Chemical structure:</p>  <p>Molecular formula: C₆H₁₁NO₂</p> <p>Molecular weight: 129.16</p>
Poisons Standard name	N/A
Applicant	Department of Health, WA
Application/Proposal type	New entry: Alkyl nitrites group entry in Schedule 4 Amendment: Lubricants entry in Appendix A
Scheduling proposal	<p>To reduce the misuse and abuse of alkyl nitrites in inhalants/'poppers' for recreational use. Some suppliers of products containing alkyl nitrites are claiming that they are present as 'lubricants'. This proposal has two parts:</p> <ol style="list-style-type: none"> 1. Make an amendment to the Appendix A lubricant entry clarifying its use is for 'preparations that provide a lubricating action between machinery parts'; and 2. Include a group entry for volatile alkyl nitrites in Schedule 4.
Section	Scheduling Secretariat

Applicant's scheduling proposal and reasons for the proposal

In October 2017, the applicant submitted a proposal to amend the Appendix A listing of lubricants and include a group entry for alkyl nitrites in Schedule 4 of the Poisons Standard.

The applicant's proposed amendments to the Poison Standard are as follows:

Schedule 4—New Entry

ALKYL NITRITES **except** those specifically listed elsewhere in these Schedules.

Appendix A—Amend Entry

LUBRICANTS in preparations that provide a lubricating action between machinery parts, **except** soluble oils and solvent-deposited lubricating agents.

The applicant's reasons for the request are:

- There are increasing reports of misuse and abuse of 'poppers' containing short chain volatile alkyl nitrites for purposes of recreational use alongside narcotics in the clubbing/dance scene in Australia and globally.
- Information received from the applicant indicates that some suppliers of 'poppers' (which contain various short chain volatile alkyl nitrites, although not usually amyl nitrite anymore) are claiming their products are exempt from the SUSMP on the basis that they are marketed as 'lubricants'. A lubricating action is unlikely owing to the volatility of the alkyl nitrites contained in these products. The products are generally labelled as 'leather cleaners' or 'room odourisers' but there is no credible evidence they are actually used for either of these purposes. Rather the contents of the little bottles, which cost about \$30 to \$50, are inhaled.
- Ophthalmologists in Australia are reporting an increase in the number of cases of maculopathies (retinal damage) caused by recreational use of poppers/'lubricants' containing alkyl nitrites. These reports have been observed elsewhere in the world, with the first cases reported in *The New England Journal of Medicine* in 2010.
- Possible amendments to the SUSMP suggested by the applicant include either specific listing of these alternative alkyl nitrites or the crafting of an entry to ensure clarity of the intent of capturing any volatile alkyl nitrite in S4.

The application letter is at D17-847761

Current scheduling status

Five (5) alkyl nitrites are currently listed in Schedule 4 of the Poisons Standard that was in effect at the time the proposal was received (Poisons Standard March 2018 (SUSMP No. 20) as follows:

Schedule 4

AMYL NITRITE.

BUTYL NITRITE.

ISOAMYL NITRITE.

ISOBUTYL NITRITE.

OCTYL NITRITE.

Scheduling history

Amyl nitrite

In January 1955, the Committee of Poisons Schedules placed amyl nitrite in Schedule 3 of the newly created Poisons Standard. In February 1989, following reports of recreational abuse of amyl nitrite and other nitrites a change to Schedule 4 was foreshadowed. Members considered that the substance had no use in contemporary medicine, although anecdotally it was being used by the mining industry as a cyanide antidote. The Schedule 3 entry was deleted and a new Schedule 4 entry created in February 1990.

In November 1993 (deferred from August 1993), the National Drugs and Poisons Committee (NDPSC) considered a proposal to create new Appendix D (Possession of this drug without authority should be illegal) entries for amyl and butyl nitrate owing to their reported use by paedophiles, who administer it to children for anal dilation. The committee decided that due to the lack of precise information about widespread misuse by paedophiles, this proposal was not warranted at this time and that more attention should be paid to policing the illegal supply of a Schedule 4 substance.

In August 1995, the National Drugs and Poisons Committee (NDPSC) considered the use of amyl nitrite as a first-aid treatment for cyanide poisoning. The Committee considered that the use of amyl nitrite as a first aid treatment for cyanide poisoning could not be supported in view of concerns with its safety and efficacy. Consequently, it would not support any change to its current Schedule 4 status. The committee agreed that if amyl nitrite were to be used as an antidote, existing mechanisms were available in each of the States and Territories to permit such use.

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for amyl nitrite. At the time the committee noted that amyl nitrite is scheduled in NZ as Part III, but is exempted from scheduling in NZ when sold as an antidote for cyanide poisoning associated with the use of sodium cyanide for vertebrate control. The committee was advised that the Working Party while considering Schedule 4 was appropriate for amyl nitrite recognised the need for an exemption in the NZ entry to allow its availability as an antidote.

Butyl nitrite

In November 1978 a new Schedule 3 entry was created for butyl nitrite, owing to concerns that there were no controls over the substance, which was anecdotally being used as a sex stimulant. In February 1989 an amendment to Schedule 4 was foreshadowed for butyl nitrites and other nitrites. The Schedule 3 entry was deleted and a new Schedule 4 entry created in February 1990.

In November 1993 (deferred from August 1993), the National Drugs and Poisons Committee (NDPSC) considered a proposal to create new Appendix D (Possession of this drug without authority should be illegal) entries for amyl and butyl nitrate owing to their reported use by paedophiles, who administer it to children for anal dilation. The committee decided that due to the lack of precise information about widespread misuse by paedophiles, this proposal was not warranted at this time and that more attention should be paid to policing the illegal supply of a Schedule 4 substance.

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe

adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Isoamyl nitrite

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Isobutyl nitrite

In February 1989, isobutyl nitrite was among a number of alkyl nitrites being considered for inclusion in Schedule 4 following reports of recreational abuse. A Schedule 4 entry for isobutyl nitrite was created in February 1990.

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Octyl nitrite

In May 1956 the PSC created a new Schedule 3 entry for octyl nitrite. This scheduling was confirmed for all jurisdictions in February 1985. In February 1989, following reports of recreational abuse of amyl nitrite and other nitrites an amendment to a Schedule 4 entry was foreshadowed. The Schedule 3 entry was deleted and a new Schedule 4 entry created in February 1990. In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Nitrites

When considering a proposal to delete Schedule 3 entries for amyl, butyl and octyl nitrite and to create new Schedule 4 entries for these substances and also for isobutyl nitrite, the committee decided against making a generic entry for 'ALIPHATIC DERIVATIVES OF NITROUS ACID' as there was a trend away from generic scheduling entries, with specific entries being preferred.

Isopropyl nitrite, Isopentyl nitrite, propyl nitrite, cyclohexyl nitrite

Isopropyl nitrite, Isopentyl nitrite, propyl nitrite and cyclohexyl nitrite are not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Lubricants

Exemptions from scheduling were first proposed at the December 1965 Poisons Schedule Sub-Committee (PSSC) meeting. The original listing was for purposes that in some substances a poison is not likely to be released to cause poisoning. 'Motor fuels and lubricants unless

specified in Schedule 5' was first among the first list of exemptions. It was not until the January 1969 PSSC meeting that the recommendation was made to include the list of exemptions, which included 'motor fuels and lubricants'.

Australian regulations

The Australian Register of Therapeutic Goods (ARTG) has no products that contain the alkyl nitrites isopentyl nitrite, 2-pentyl and N-propyl nitrite or cyclohexyl nitrite. The current Therapeutic Goods (Permissible Ingredients) Determination No.5 of 2017 does not contain any alkyl nitrites.

According to the TGA Ingredient Database amyl nitrite, octyl nitrite and nitrite are available for use as active ingredients in biologicals and prescription medicines, and excipient ingredients in biologicals, devices and prescription medicines;

There are no agricultural and veterinary chemicals containing any nitrite listed on the APVMA's PubCRIS.

International regulations

The international legal status of alkyl nitrites is unclear. In the EU isobutyl nitrite was classified as a class 2 carcinogen under the EU Directive 76/769/EEC, making it illegal for shops to sell this variety of poppers.

In January 2016 the UK government included alkyl nitrites in a list of banned psychoactive substances, but this decision was set to be reviewed, and it is unclear whether this decision remains.

In New Zealand, amyl nitrite is a prescription medicine **except** when sold to a person who holds a controlled substances licence (issued under section 95B of the Hazardous Substances and New Organisms Act 1996) authorising the person to possess cyanide and **except** when sold to an exempt laboratory covered by a Hazardous Substances and New Organisms Act 1996 approved code of practice. Octyl nitrite, isobutyl nitrite, butyl nitrite and isoamyl nitrite are classified as prescription medicines.

Substance summary

Please see application, available at [D17-847761](#), [D18-10371910](#).

'Poppers' is the street term for various alkyl nitrites taken for recreational purposes through direct inhalation. In the past these included amyl nitrite, butyl nitrite and isobutyl nitrite, with more recent variations including isopropyl and cyclohexyl nitrite. Alkyl nitrites have a smooth muscle relaxant effect, and were first used therapeutically (amyl nitrite) to treat angina. They have been used as recreational drug for the reported sensations of head rush, euphoria, uncontrollable laughter or giggling, and other sensations that result from the hypotensive effect and increase sexual arousal and desire. In addition, the smooth muscles of the anus and vagina are relaxed. Adverse effects of short term use include severe headache, throat irritation, nose bleeds, nausea, erectile problems, sensations of spinning or falling and dyspnoea. According to St George's Hospital, University of London, there have been 14 deaths in the UK related to inhaling alkyl nitrites since 1971, three of which were in 2006⁷.

In Australia, the drugs are sold under the guise of room deodorisers and cleaning solvents, and are readily available in adult shops and online. NDARC's Ecstasy and Related Drugs Reporting

⁷ <http://www.re-solv.org/wp-content/uploads/2011/12/Poppers.pdf>

System (EDRS) shows use of amyl nitrite (which may include other alkyl nitrites) running at 27% of those who participated in the survey in 2016 (up from 21% in 2015)⁸. The demographics of the survey group suggest popper use has expanded to the community more generally – it was once associated more with the LGBTI community.

Ophthalmologists in Australia are seeing an increase in cases of temporary and permanent macula damage caused by recreational drug use of alkyl nitrite compounds. Ophthalmologists believe that chronic use could lead to irreversible damage. Alkyl nitrite ‘popper’ maculopathy causes gradual vision loss and clinically is the equivalent of having a hole burned in the macula from gazing at the sun.

Scheduling issues – to the delegate only

Amending the Appendix A definition of ‘lubricant’ was proposed as this has been claimed by a supplier of a ‘leather cleaner’ in [REDACTED]

There are many products currently being marketed as ‘room odorisers’. Including a Schedule 4 general entry for ‘alkyl nitrites’ could allow action to be taken against suppliers of these products.

Recommendations

R1. That you decide to consider this matter as a delegate-only decision.⁹

AGREE
DISAGREE

*Reasons**: Requires advice from ACMS/ACCS

R2. That you decide to refer this matter to the ACCS-ACMS

AGREE
DISAGREE

*Reasons**: Needs advice due to broad use.

If you refer this matter to ACMS/ACCS-ACMS, please provide specific issues/questions you wish the committee/s to consider:

- What is the appropriate wording for S4 and Appendix A to ensure that the intent is clear?

R3. That you decide that the application requires an external evaluation.

AGREE
DISAGREE

*Reasons**: [delegate to insert reason]

R4. That you decide to the draft public notice as follow:

SUBSTANCE	SCHEDULING PROPOSAL
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⁸

https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/National_EDRS_%202016_FINALwith%20customs.pdf

⁹ Please note that by accepting this recommendation the delegate is not making an interim decision or final decision

Alkyl nitrites	CAS Number	N/A (group entry)
		<p>Examples of volatile alkyl nitrites not listed in the Poisons Standard include:</p> <ul style="list-style-type: none"> • 110-46-3, isopentyl nitrite (nitrous acid, 3-methylbutyl ester, isoamyl nitrite) • 541-42-4, 2-propyl nitrite (IUPAC) synonyms: isopropyl nitrite, isopropyl alcohol nitrite, nitrous acid, isopropyl ester, 1-methylethyl nitrite, 2-propyl nitrite • 543-67-9, <i>N</i>-propyl nitrite, Propyl nitrite; Propanol nitrite; Nitrous acid, propyl ester; <i>N</i>-Propyl-nitrite • 5156-40-1, cyclohexyl nitrite (IUPAC) (nitrous acid, cyclohexyl ester; <i>N</i>-cyclohexyl nitrite; cyclohexyl alcohol nitrite; <i>C</i>-hexyl nitrite; <i>O</i>-nitrosocyclohexanol)
	Applicant	Delegate initiated
	Current scheduling	Five (5) alkyl nitrites (amyl nitrite, butyl nitrite, isoamyl nitrite, isobutyl nitrite and octyl nitrite) are currently listed in Schedule 4 of the Poisons Standard.
	Proposed scheduling	<p>To reduce the misuse and abuse of alkyl nitrites in lubricants and inhalants/'poppers' for recreational use by amending the Appendix A entry for lubricants to clarify use for 'preparations that provide a lubricating action between machinery parts' and to include a group entry for volatile alkyl nitrites in Schedule 4, as follows:</p> <p>Schedule 4—New Entry</p> <p>ALKYL NITRITES except those specifically listed elsewhere in these Schedules.</p> <p>Appendix A—Amend Entry</p> <p>LUBRICANTS in preparations that provide a lubricating action between machinery parts, except soluble oils and solvent-deposited lubricating agents.</p>
	Key uses / expected use	Medicines and industrial use
	Reasons for proposal	<ul style="list-style-type: none"> • There are increasing reports of misuse and abuse of 'poppers' containing short chain volatile alkyl nitrites for purposes of recreational use alongside narcotics in the clubbing/dance scene in Australia and globally. • Some suppliers of products containing alkyl nitrites for illicit use are claiming that these substances are used for their lubricant properties and are therefore exempt from scheduling.

		<ul style="list-style-type: none">Ophthalmologists in Australia are reporting an increase in the number of cases of maculopathies (retinal damage) caused by recreational use of poppers/'lubricants' containing alkyl nitrites. These reports have also been observed internationally.
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AGREE
DISAGREE

Reasons*: [delegate to insert reason].

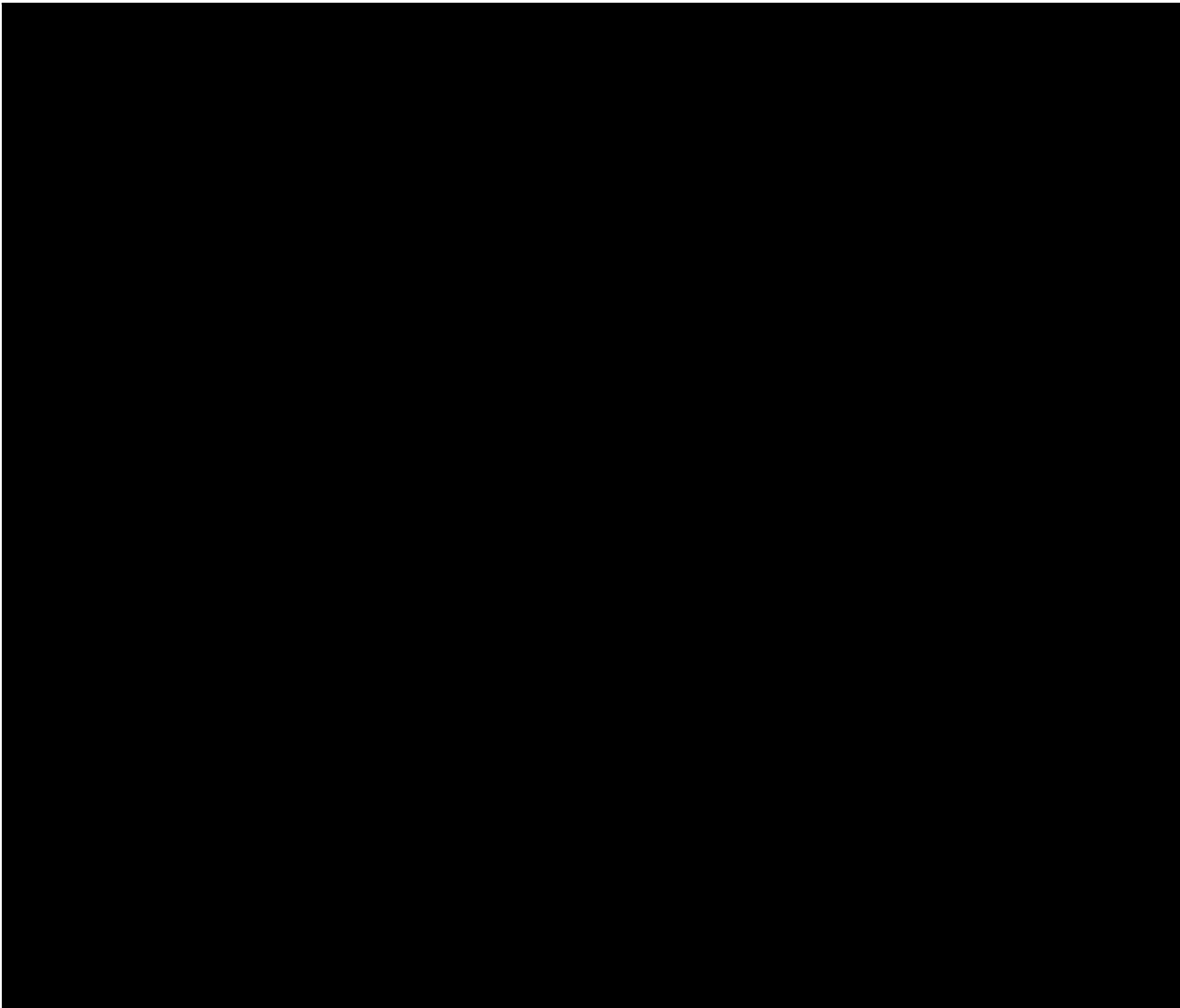
Authorised for electronic submission

Medicines Scheduling Delegate

4 April 2018

Attachments

Attachment A: Application ([D17-847761](#), [D18-10371910](#))



Notes – pages 61 to 64 inclusive do not relate to alkyl nitrites and have been redacted as irrelevant under s 22(1) of the FOI Act
