

SUBMISSION FOR RECLASSIFICATION

HYOSCYAMINE

HYOSCINE

HYOSCYAMUS

WELEDA NEW ZEALAND LTD.

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HAVELOCK NORTH

RATIONALE

Preamble

The recent recommendation to set an exemption from scheduling levels has occurred as a result of the move towards harmonisation with Australian schedules. The exemption level set has implications for some homoeopathic medicines that are on the market in New Zealand, that are produced differently to homoeopathic medicines on the market in Australia.

Our aim in this submission is:

- To clarify the classification and schedule exemption levels so that they can be clearly and objectively applied to anthroposophical and homoeopathic medicines.
- To propose classification and schedule exemption levels based on active principle concentration.
- To propose classification and schedule exemption levels that fairly reflect the actual risk of the medicine to the consumer.

To our knowledge, there have been no reports of adverse effects associated with anthroposophical or homoeopathic medicines containing hyoscyamus that have initiated this change.

Rationale 1: Classification of plant substances on active principles

Classification that is based only on the plant name could severely disadvantage some homoeopathic medicines. We consider that the most effective means to classify plant substances is to base the classification criteria on the “active principle” (usually alkaloids) concentration of the plant, where possible.

This would avoid the major discrepancies in alkaloid concentration and toxicity that exist between medicines made from fresh or dry plant and different plant parts, especially homoeopathic medicines. (*Refer Appendix 2*)

It would also avoid the differences in alkaloid concentration that can occur as a result of different manufacturing and extraction processes used in the preparation of herbal substances. (*Refer Reference Copy 2*)

As can be seen from Appendix 2, a “homoeopathic potency” of a plant made following one homoeopathic pharmacopoeia would contain quite different levels of alkaloids and therefore different toxicity to the same “homoeopathic potency” of a plant produced following another pharmacopoeia. Using aconite as an example:

- **Dry Plant:** The highest alkaloid concentration of hyoscyamus, mentioned, is a dry leaf total alkaloid concentration of 0.15%. (*Refer Appendix 1, point 4.*)
Hyoscyamus mother tincture made following the Homoeopathic Pharmacopoeia of the United States, although made from fresh plant contains the equivalent of 10% of

the dry plant material and is called a 1x (10%) potency. (Refer Appendix 2)
This 1x (10% of dry plant) potency would contain a maximum of 0.015% alkaloids.

- Fresh plant: Hyoscyamus mother tincture (50% fresh whole plant juice), made following the German Homoeopathic Pharmacopoeia, contains not less than 0.007 and not more than 0.01 per cent of alkaloids, calculated as hyoscyamine (Refer Appendix 1, point 5.).
A 1x (10% of the fresh plant juice) potency made from this mother tincture would contain a maximum of 0.002% alkaloids.

As can be seen from the above two points, there is just under a **ten fold** difference in the hyoscyamine concentration of homoeopathic potencies originating from methods based either on a dry plant concentration or a fresh plant juice concentration.

Medsafe Precedents: Previous wording of the Medsafe classification of plants referred to the percentage strength of the alkaloids of the plant, eg. Aconite; alkaloids of and salts, except in medicines containing less than 0.02% of the alkaloids of Aconite.

Australian Precedents: Many of the classifications of herbs in the Australian Standard for the Uniform Scheduling of Drugs and Poisons refer to the percentage strength of the alkaloids of the plant, eg. Schedule 2 (Pharmacy Medicine) BELLADONNA, in preparations containing 0.25 per cent or less of the alkaloids of belladonna.

We consider that classification of plant medicines based on the active principle concentration removes the “grey” areas inherent in the present system. It provides objective and clear limits to use when classifying products.

Rationale 2: Reclassification

We presume that the rationale behind the present classification based on solid and liquid dose forms relates to safety, but this does cause a problem for low concentration, homoeopathic medicines that are commonly presented in liquid form. These low concentration products do not pose the same safety issues that a conventional product may pose.

We propose a cut-off level for the liquid and powder preparations to address this situation based on a pack containing the dose used in the classification of 0.3 milligrams, being a single therapeutic dose.

Therapeutic dose: Dose range: 0.15 mg to 0.3 mg hyoscyamine
(Refer Appendix 1, point.8.)

Proposed reclassifications – refer Part A, Point 8.

PhOM: Hyoscyamine, Hyoscine, or Hyoscyamus, **alkaloids of; for oral use in liquid or powder form in a pack containing more than 0.3 milligrams;**

PM: Hyoscyamine, Hyoscine, or Hyoscyamus, **alkaloids of; for oral use in liquid or powder form in a pack containing 0.3 milligrams or less;**

The effect of this reclassification is that:

Liquid or powder oral preparations in a pack containing more than a single therapeutic dose of 0.3 mg of hyoscyamine, hyoscine or the alkaloids of hyoscyamus are classified as Pharmacist Only Medicines.

Liquid or powder oral preparations in a pack containing a single therapeutic dose of 0.3 mg or less of hyoscyamine, hyoscine or the alkaloids of hyoscyamus are classified as Pharmacy Medicines.

Rationale 3: Schedule exemption level based on active principle concentration

The aim is:

To provide an exemption level for hyoscyamus based on the alkaloid concentration, not the plant name.

To provide an exemption level that is consistent with the exemption levels for belladonna.

To provide a 1000 fold difference between a therapeutic dose and the dose of a product containing the exemption level.

Exemption levels consistent with belladonna exemption levels

(refer to Belladonna Reclassification Submission)

The accepted exemption level of belladonna in Appendix G in the Australian Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) is belladonna 10 mg/L/kg, which is equivalent to 100 micrograms per litre or per kilogram of the alkaloids of belladonna (usually calculated as hyoscyamine). This provides a wide safety margin of a **1000 fold** difference between the therapeutic dose range (0.15 mg to 0.3 mg) and the dose of a product containing the exemption level (0.0001 mg).

This is different to the exemption level in Appendix G of the SUSDP for hyoscyamine and hyoscine which is set at 10 micrograms per litre or per kilogram. Considering that belladonna has been set at an exemption level that results in the actual exemption being 100 micrograms per litre or per kilogram of the alkaloids of belladonna (usually calculated as hyoscyamine) without any reported safety issues, we would propose that the same exemption level be applied to hyoscyamine, hyoscine and the alkaloids of Hyoscyamus.

Proposed schedule exemption – refer Part A, Point 8.

Hyoscyamine, Hyoscine or Hyoscyamus, in preparations containing 100 microgram per litre or per kilogram of hyoscyamine, hyoscine or the alkaloids of hyoscyamus (0.00001%)

(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten.)

The proposed schedule exemption level provides an exemption level that is consistent with the exemption levels for belladonna.

Therapeutic dose: Dose range: 0.15 mg to 0.3 mg hyoscyamine
(Refer Appendix 1, point 8.)

A 1 mL oral dose of a product containing the proposed schedule exemption of 0.00001% hyoscyamine, hyoscine or the alkaloids of hyoscyamus would contain 0.0001 mg alkaloids.

This is more than a **1000 fold** difference between the therapeutic dose range (0.15 mg to 0.3 mg) and the dose of a product containing the exemption level (0.0001 mg).

We consider that this is an extremely wide safety margin.

An exemption level based on the alkaloid concentration would prevent inequities occurring because of differences in alkaloid concentration of “homoeopathic potencies” made following different homoeopathic pharmacopoeia (refer Appendix 2).

As pointed out in Rationale 1.:

1x (10% of dry plant) potency would contain a maximum of 0.015% alkaloids
1x (10% of the fresh plant juice) would contain a maximum of 0.002% alkaloids.

Present schedule exemption level of hyoscyamus plant at 10 mg/L/kg (0.001%) would result in:

- Hyoscyamus, dry plant 5x (0.001%) containing a maximum of 0.0000015% alkaloids **being exempt from classification.**
- Hyoscyamus, fresh plant juice 4x (0.01%) containing a maximum of 0.000002% alkaloids **being classified.**

At present the exemption level would result in one product being exempt from classification, whilst a product containing only 0.0000005% more alkaloids would be classified.

Proposed schedule exemption of alkaloids of hyoscyamus at 100 microgram/L/kg (0.00001%) results in:

- Hyoscyamus, dry plant 5x (0.001%) containing a maximum of 0.0000015% alkaloids **being exempt from classification.**
- Hyoscyamus, fresh plant juice 4x (0.01%) containing a maximum of 0.000002% alkaloids **being exempt from classification.**

This proposed exemption level would result in two products that both contain a concentration of alkaloids that is below the exempt level being classified in the same way, i.e. exempt.

Rationale 4: Safety in the market place

Weleda medicines containing hyoscyamus have been on the market since the early 1950's and have had wide use during those years, in the customer base to which they are directed. There have been NO adverse reactions reported.

PART A

1. International Non-proprietary Name of the medicine

Hyoscyamus

2. Proprietary name(s)

Non-specific change application for anthroposophical and homoeopathic products.

3. Company requesting reclassification

Weleda New Zealand Ltd.
P.O. Box 8132
Havelock North
NEW ZEALAND

4. Dose form(s) and strength(s)

Not applicable.

5. Pack size and other qualifications

Not applicable.

6. Indications for which change is sought

Not applicable.

7. Present classification of medicine

Prescription Only Medicine: Hyoscyamine; for injection or ophthalmic use

Pharmacist Only Medicine: Hyoscyamine; in liquid form for oral use; in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose

Pharmacy Medicine: Hyoscyamine; in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose

General schedule exemption: Hyoscyamine at 10 mg per litre or per kilogram

Prescription Only Medicine: Hyoscine; for injection or ophthalmic use

Pharmacist Only Medicine: Hyoscine; for transdermal use; for oral use in liquid form; in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose

Pharmacy Medicine: Hyoscine; in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose

General schedule exemption: Hyoscine at 10 mg per litre or per kilogram

8. Classification sought

Prescription Only Medicine: Hyoscyamine; for injection or ophthalmic use

Pharmacist Only Medicine: Hyoscyamine; **for oral use in liquid or powder form in a pack containing more than 0.3 milligrams;** in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose

Pharmacy Medicine: Hyoscyamine; **for oral use in liquid or powder form in a pack containing 0.3 milligrams or less;** in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose

Schedule exemption: **Hyoscyamine, in preparations containing 100 micrograms per litre or per kilogram of hyoscyamine (0.00001%)**
(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten.)

Prescription Only Medicine: Hyoscine; for injection or ophthalmic use

Pharmacist Only Medicine: Hyoscine; for transdermal use; **for oral use in liquid or powder form in a pack containing more than 0.3 milligrams;** in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose

Pharmacy Medicine: Hyoscine; **for oral use in liquid or powder form in a pack containing 0.3 milligrams or less;** in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose

Schedule exemption: **Hyoscine, in preparations containing 100 micrograms per litre or per kilogram of hyoscine (0.00001%)**
(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten.)

and to add in a classification for Hyoscyamus.

Pharmacist Only Medicine: Hyoscyamus, **alkaloids of; for oral use in liquid or powder form in a pack containing more than 0.3 milligrams;** in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose

Pharmacy Medicine: Hyoscyamus, **alkaloids of; for oral use in liquid or powder form in a pack containing 0.3 milligrams or less;** in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose

Schedule exemption: **Hyoscyamus, in preparations containing 100 micrograms per litre or per kilogram of the alkaloids of hyoscyamus (0.00001%)**
(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten.)

9. Classification status in other countries

Germany: *Prescription Only Medicine:* Hyoscyamus up to and including D3 (3x; 0.1%)

Australia: Hyoscyamus
Schedule 4 (Prescription Only Medicine):
HYOSCYAMUS **except** when included in Schedule 2.
Schedule 2 (Pharmacy Medicine):
HYOSCYAMUS in preparations containing 0.25% or less of the alkaloids of hyoscyamus.
Schedule exemption: 10 mg per litre or per kilogram

Australia: Hyoscyamine

Schedule 4 (Prescription Only Medicine):

HYOSCYAMINE **except** when included in Schedule 2.

Schedule 2 (Pharmacy Medicine):

HYOSCYAMINE in preparations containing 0.25% or less of hyoscyamine.

Schedule exemption: 10 micrograms per litre or per kilogram

Australia: Hyoscine

Schedule 4 (Prescription Only Medicine):

HYOSCINE **except** when included in Schedule 2.

Schedule 2 (Pharmacy Medicine):

HYOSCINE in preparations containing 0.25% or less of hyoscine; or in transdermal applications containing 2 mg or less of hyoscine.

Schedule exemption: 10 micrograms per litre or per kilogram

10. Extent of usage in NZ and elsewhere

Homoeopathic preparations of Hyoscyamus are commonly used by homoeopaths and manufactured by most homoeopathic manufacturers.

11. Proposed labelling

Not applicable.

12. Proposed warning statements

Not applicable.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

Anthroposophical and homoeopathic medicines.

PART B

Reasons for Requesting Classification Change

1. Expected benefits to both the consumer and to the public

Maintains accessibility to safe anthroposophical and homoeopathic medicines that have been used for minor, self-limiting conditions, in NZ for more than 40 years.

2. Ease of self-diagnosis or diagnosis by a pharmacist

Not applicable.

3. Relevant comparative data for like compounds

Not applicable

4. Local data or special considerations relating to NZ

Not applicable

5. Interactions with other medicines

None known.

6. Contraindications

Not applicable.

7. Possible development of drug resistance

None

8. Adverse events

Weleda medicines containing hyoscyamus have been on the NZ market since the early 1950's and on the European market since the early 1920's. During these years there have been, to our knowledge, no reports of any adverse events associated with these anthroposophical and homoeopathic medicines.

9. Potential for abuse or misuse

None

Glossary, Appendices and Reference Copies

Glossary

Anthroposophical medicine

The medicines specially made for anthroposophical therapy which contain herbal and homoeopathically produced preparations.

Homoeopathic medicine

Article 1 of the European Guidelines EG 92/73 and EG 92/74 on Homoeopathic Pharmaceuticals for Human respectively Veterinary Use provides the following definition [official within the 15 nations of the E.U.] of the term “homoeopathic medication”:

(1) ”Within the sense of this Guideline, a homoeopathic (veterinary) medication constitutes any medicinal agent, which has been prepared from products, substances, or compounds designated as homoeopathic source-material in accordance with homoeopathic manufacturing procedure as described in a European pharmacopoeia or – in absence of the corresponding monograph – according to the currently official pharmacopoeia of a member state.

(2) “Homoeopathic medication may contain multiple active constituents”
[Official Journal of European Communities No. L 297/8 of Oct.13, 1992].

Homoeopathic medicines can be the mother tincture right through the range of homoeopathic potencies.

Homoeopathic potency

A homoeopathic potency is produced from one or several source material or mother tinctures, generally followed by potentising: serial dilution and succussion (potentisation). The following are examples of the common attenuation-ratios:

- 1:10 - Decimal or D, DH, or X potencies
- 1:100 - Centesimal or C, CH potencies
- 1:50,000 - Q or LM potencies

Potentisation

Potentisation: serial dilution and succussion - a special form of shaking the liquid dilution, or triturating the powder dilution.

Mother tincture

A mother tincture is a preparation of a substance, that is used as the starting material for the preparation of a homoeopathic potency, and in some cases can also be used as a homoeopathic medicine in its own right.

Appendices

1. Appendix 1: References to Active Principle, Therapeutic and Toxicity Levels
2. Appendix 2: Concentration Differences Between Homoeopathic Medicines Using Aconite as an Example
3. Appendix 3: Previous Medsafe classifications of Hyoscyamine and Hyoscine

Reference Copies

1. Reference Copy 1: pg. 405-406, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
2. Reference Copy 2: Aconite Monograph date of issue: Feb.1993, The Lawrence Review of Natural Products – Monograph System, published by Fact and Comparisons, ISSN 0734-4961
3. Reference Copy 3: pg. 103, German Homoeopathic Pharmacopoeia (GHP) (Homoopathisches Arzneibuch HAB) Official Edition, published by Deutscher Apotheker Verlag Stuttgart Govi-Verlag GmbH, Frankfur, ISBN 0946717 05 2, ISBN for German original 3-7692-0932-X
4. Reference Copy 4: pg. 351-353, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
5. Reference Copy 5: pg. 146, The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines, by Blumenthal, Buse, Goldberg, Gruenwald, Hall, Klein, Riggins & Rister, published in cooperation with Integrative Medicine Communications, ISBN 0-9655555-0-X
6. Reference Copy 6: pg. 1275, Medical Toxicology, Diagnosis and Treatment of Human Poisoning (1988), by Matthew J. Ellenhorn and Donald G. Barceloux, published by Elseveier Science Publishing Company, Inc., ISBN 0-444-01129-3
7. Reference Copy 7: pg. 531, German Homoeopathic Pharmacopoeia (GHP) (Homoopathisches Arzneibuch HAB) Official Edition, published by Deutscher Apotheker Verlag Stuttgart Govi-Verlag GmbH, Frankfur, ISBN 0946717 05 2, ISBN for German original 3-7692-0932-X
8. Reference Copy 8: pg. 427, Martindale, 30th Ed., published by The Pharmaceutical Press, ISBN 0 85369 300 5, ISSN 0263-5364