SUBMISSION FOR RECLASSIFICATION

SOLANACEOUS PLANTS AND ALKLAOIDS

ATROPA BELLADONNA

ATROPINE

HYOSCINE

HYOSCYAMINE

HYOSCYAMUS NIGER

Request for a change to the level for exemption from scheduling

For the 28th MCC Meeting

WELEDA NEW ZEALAND LTD.

P.O. BOX 8132

HAVELOCK NORTH

RATIONALE

Preamble

This submission is to request a change to the level for exemption from scheduling for the solanaceous alkaloids, particularly those of the plants Atropa belladonna and Hyoscyamus niger, eg. atropine, hyoscine and hyoscamine, to be addressed in this submission in the wider context of the solanaceous plants and alkaloids.

The original Weleda submission, to the 25th MCC meeting May 2001, requested modification to the cut-off points for pharmacy-only medicines and a change to the level for exemption from scheduling. Consideration of the original submission was delayed due to recommendations from the NDPSC and these were finally considered at the 27th Meeting of the MCC, May 2002, Item 8.5.5 Solanaceous plants and alkaloids. The outcome of this meeting only addressed amendments to the pharmacy-only medicine classification of these substances and did not address the second request to consider a change to the level for exemption from scheduling.

There are a number of reasons for this request:

1. The present NZ general level for exemption from scheduling, of 10mg per litre or kilogram, that would be applied to hyoscine and hyoscyamine appears to be too concentrated, and the present cut-off point for atropine, 100 micrograms per litre or kilogram, appears to be too dilute and not substantiated by toxicity data.
2. The proposed amendments from the 27th MCC meeting have grouped the solanaceous plants and alkaloids together and have applied the same pharmacy-only medicine cut-off points to the group.
   It would seem appropriate to apply the "grouping" approach, used for the pharmacy-only medicine cut-off point for the solanaceous alkaloids, to the level for exemption from scheduling for all the solanaceous alkaloids.
3. To ensure that the cut-off point relates to the alkaloids of these solanaceous plants rather than the plants themselves as the alkaloid concentration varies in the plants.

It may help to give some background to the Weleda submissions. Weleda makes a range of medicines, some herbally based and many homoeopathically based. The main focus in our submissions has been on the x-potency (1 in 10 dilution) homoeopathic range. The homoeopathic substances are used in potencies that range from 1x (10%), 2x (1%), 3x (0.1%) through to 30x (10^{-30}). Each potency can either be used as a single remedy, e.g. Belladonna 4x, or used in a complex with other potentised substances.

[Potency is the term used to describe each dilution (either 1 in 10 x-potency or 1 in 100 c-potency dilutions) and succussion (special shaking) production step.]

Therefore when considering an approach to scheduling we were more interested in where cut-of points might occur along the potency range. Consequently our efforts are to try and identify some rationale that could underpin cut-off points as they applied generally to concentrations of substance rather than to specific medicines. We understand that this is not the usual approach and will try to address this in this submission but we do want to flag that our submission is trying to address more than just one or two products.

PART A

1. International Non-proprietary Name of the medicine

Solanaceous plants and alkaloids: Atropa belladonna, Hyoscine, Hyoscyamine, Hyoscyamus niger

2. Proprietary name(s)

Belladonna homoeopathic potencies and strengths used by Weleda
1x, 2x, 3x, 4x, 5x, 6x, 8x, 10x, 12x, 15x, 20x, 30x
Hyoscyamus homoeopathic potencies and strengths used by Weleda
1x, 2x, 3x, 4x, 5x, 6x, 8x, 10x, 12x, 15x, 20x, 30x
Some of these potencies are contained in a few Weleda OTC medicines, eg. Hyoscyamus at a 3x strength, 0.1%, and the rest are available as single potencies, either OTC or prescribed by practitioners.

3. Company requesting reclassification

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

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

Dose form: Internal homoeopathic medicines are available in a variety of dose forms: liquid, powder, pilules, tablets

Bold Lines: In the following tables the proposed cut-off point, 0.03mg (30 micrograms) per pack size, would operate at the point of the bold lines in the tables.

Belladonna - strength of total alkaloids
Max. total alkaloids in fresh plant = 0.07% *(refer Appendix 1, point 7)*

Belladonna Potency	**Whole plant concentration**	**Alkaloid concentration**	**mg total alkaloids/100mL**
100%	100%	0.07%	NA
2x	1%	0.0007%	0.7mg/100mL
3x	0.1%	0.00007%	70mcg/100mL
4x	0.01%	0.000007%	7mcg/100mL
5x	0.001%	0.0000007%	0.7mcg/100mL

Hyoscyamus - strength of total alkaloids
Max. total alkaloids in fresh plant = 0.02% *(refer Appendix 1, point 12)*

Hyoscyamus Potency	Whole plant concentration	Alkaloid concentration	mg total alkaloids/100mL
100%	100%	0.02%	NA
1x	10%	0.002%	2mg/100mL
2x	1%	0.0002%	0.2mg/100mL
3x	0.1%	0.00002%	20mcg/100mL
4x	0.01%	0.000002%	2mcg/100mL
5x	0.001%	0.0000002%	0.2mcg/100mL

5. Pack size and other qualifications

Liquids: 30mL, 100mL – glass bottles with tamper evident caps.
Solids: 30g – glass jar with tamper evident cap.

6. Indications for which change is sought

Belladonna in a variety of potencies is prescribed by homoeopathic and anthroposophical practitioners for a variety of conditions.
Belladonna is an ingredient in a variety of Weleda OTC medicines used for conditions that have an inflammatory component, eg. skin inflammation in bee stings, etc.

Hyoscyamus in a variety of potencies is prescribed by homoeopathic and anthroposophical practitioners for a variety of conditions.
Hyoscyamus is an ingredient in a variety of Weleda OTC medicines some of which are used to help relieve nausea and vomiting eg. travel sickness, seasickness, jetlag.

We consider that these are minor and self-limiting conditions.

7. Present classification of medicine

(as per proposed amendments from the 27th MCC meeting – as the wording is not yet finalized we presume that the wording will be similar to that already used in the schedules)

<u>Prescription Medicine:</u>
Atropa belladonna (belladonna) except when specified elsewhere in this Schedule.
Hyoscyamus niger except when specified elsewhere in this Schedule

Pharmacy-only Medicine:

Atropa belladonna (belladonna) for oral use:

(i) in undivided preparations containing 0.03% or less of the alkaloids of belladonna when labelled with a dose of 0.3mg or less of the alkaloids of belladonna and a recommended daily dose of 1.2 mg or less of the alkaloids of belladonna: or

(ii) in divided preparations containing 0.3 mg or less of the alkaloids of belladonna per dosage unit, when labelled with a recommended daily dose of 1.2 mg or less of the alkaloids of belladonna

Hyoscyamus niger for oral use:

(i) in undivided preparations containing 0.03% or less of the alkaloids of hyoscyamus when labelled with a dose of 0.3mg or less of the alkaloids of hyoscyamus and a recommended daily dose of 1.2 mg or less of the alkaloids of hyoscyamus: or

(ii) in divided preparations containing 0.3 mg or less of the alkaloids of hyoscyamus per dosage unit, when labelled with a recommended daily dose of 1.2 mg or less of the alkaloids of hyoscyamus

General Sale Medicine:

Unless specific reference is made otherwise, every reference to a medicine in the schedules applies –

(i) …….

(ii) …… , only if the concentration of the medicine is greater than 10 milligrams per litre or per kilogram.

i.e. unless otherwise stated a medicine is exempt from scheduling if the concentration of the medicine is equal to or less than 10mg per litre or per kilogram.

8. Classification sought

General Sale: Solanaceous alkaloids (eg. alkaloids of Belladonna and Hyoscyamus)

- for oral use in packs containing 0.03mg or less of total solanaceous alkaloids.

The following concentration references have been used

- Fatal dose: 3mg has been used as the fatal dose, being somewhere between 1.6mg and 10mg atropine for a child. *(refer Appendix 1, point 13. and 14.)*
- Therapeutic dose: 0.3mg has been used as the therapeutic dose, being the dose referred to in the proposed pharmacy-only medicine classification as well as being in the dose range recommended by Martindale, being 0.15 mg to 0.3 mg. *(refer Appendix 1, points 15. to 20.)*

Substantiation for re-classification

- We consider that the present level for exemption from scheduling, "10mg, or less, of a medicine per litre or per kilogram" is too concentrated to apply to the solanaceous alkaloids of hyoscine and hyoscyamine – this could allow a 100mL container to contain 1mg of solanaceous alkaloids which is

equivalent to approximately 3 single doses of 300mcg or one daily dose of solanaceous alkaloids.

- At present, in NZ, atropine has a 100 microgram per litre or kilogram cut-off point - we consider that this cut-off point provides an extremely wide safety margin. Considering that most pack sizes would not be greater than 100mL this would equate to 10mcg per 100mL pack size.

- We think that it would be appropriate to apply the "grouping" approach, used for the pharmacy-only medicine cut-off point for the solanaceous alkaloids, to the level for exemption from scheduling for the solanaceous alkaloids.

- In Australia, the SUSDP Appendix G general sale cut-off point for atropine, hyoscine and hyoscyamine differ:
    - Atropine = 100mcg per litre or kilogram
    - Hyoscine = 10mcg per litre or kilogram
    - Hyoscyamine = 10mcg per litre or kilogram
- Considering that most pack sizes would not be greater than 100mL this would equate to either 10mcg or 1 mcg per 100mL pack size.
  We consider that this cut-off point provides an extremely wide safety margin and is not substantiated by toxicity data, and that also the cut-off points for these substances should be the same.

- We have therefore, once again, applied the principles of the previously discussed herbal framework to the general sale medicine cut-off point, the proposal being "for oral use in packs containing 0.03mg or less of total solanaceous alkaloids".

- This would mean that the pack size of "0.03mg or less of total alkaloids" would contain approximately 1% ($1/100^{th)}$ or less of the fatal dose (3mg) (note that this fatal dose has an extra safety factor in that it is for a child not an adult);

- and, the pack size of "0.03mg or less of total alkaloids" means that a pack can contain only 10% ($1/10^{th}$), or less, of a therapeutic dose. This ensures that no one could use a product with a general sale exemption in a conventional way. They would need to purchase 10 containers of product to achieve a conventional therapeutic dose.

- Regarding the dosage, the common dosage used for Weleda liquid products is 15 drops, approximately 1mL. Therefore if a pack size of 100mL contained 0.03mg total alkaloids a 1mL dose would contain 0.0003mg, 0.3mcg, total alkaloids – $1/1000^{th}$ of a therapeutic dose.

- In conclusion we would suggest that if the pack size concentration is not delivering a conventional therapeutic dose, and if there is no risk from acute

or chronic toxicity, then there are no safety issues and a general sale exemption should apply at the proposed concentration.

- It is important to note the different concentrations of alkaloids between plant varieties and fresh or dry plant status - this highlights the importance of cut-off points for plants being based on active principles.

    - Atropa belladonna fresh whole plant = 0.07% max. total alkaloids *(refer Appendix 1, point 7)*
      Hyoscyamus niger fresh whole plant = 0.02% max. total alkaloids *(refer Appendix 1, point 12)*
      Atropa belladonna dry root = 1% max. total alkaloids *(refer Appendix 1, point 1)*
      Hyoscyamus niger dry plant = 0.15% max. total alkaloids *(refer Appendix 1, point 11)*

9. Classification status in other countries

Australia

SUSDP, No. 17 – general exemption, pg. 7 to 8: "(2) Unless the contrary intention appears a reference to a substance in a schedule or an appendix to this Standard includes …….
but does not include:
(i) any other substance included in Schedules 1 to 6, at a concentration not exceeding 10 mg per litre or 10 mg per kilogram, ……"
This general exemption would apply to the plants of:

Atropa belladonna
Hyoscyamus niger

i.e. the plant would be exempt at 10mg per litre or kilogram.

Depending on the plant part and whether the plant is fresh or dry, there would be a variety of actual alkaloid concentrations if this is applied, and some of the alkaloid concentrations would not comply to the Appendix G level for the alkaloids, eg.

10mg Atropa belladonna fresh whole plant, max. alkaloids 0.07%	= 7mcg
10mg Hyoscyamus niger fresh whole plant max. alkaloids 0.02%	= 2 mcg
10mg Atropa belladonna dry root max. alkaloids 1%	= 100mcg
10mg Hyoscyamus niger dry plant max. alkaloids 0.15%	= 15mcg

SUSDP – Appendix G exemptions: The requirements of this Standard do not apply to a poison listed in Column 1 of this Appendix at a concentration not more than that specified in Column 2 in respect of that poison.

Atropine	100 micrograms per litre or kilogram
Hyoscine	10 micrograms per litre or kilogram
Hyoscyamine	10 micrograms per litre or kilogram

We consider that these cut-off points provide an extremely wide safety margin and are not substantiated by toxicity data.

10. Extent of usage in NZ and elsewhere

Weleda medicines providing the range of potencies, including Belladonna in potencies of 3x and 6x, and Hyoscyamus in potencies of 3x, have been available, as OTC products, in New Zealand for over 40 years and in Germany for over 80 years. These products are also sold in many other countries - there are approximately 26 Weleda companies world wide, eg. United Kingdom, South Africa, etc.

11. Proposed labelling

Copies of draft labels for Belladonna 3x and Belladonna 4x are contained in Appendix 2.

12. Proposed warning statements

If symptoms persist, consult your health care professional.
Keep all medicines out of reach of children

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

Other homoeopathic medicines containing Belladonna and Hyoscyamus potencies.

PART B

Reasons for Requesting Classification Change

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

The proposed exemption allows easy access, via health food shops and pharmacies, to commonly used homoeopathic potencies of Belladonna and Hyoscyamus by homoeopathic and anthroposophical practitioners and their patients.
Skin inflammations like bee stings, travel sickness, seasickness and jetlag are common, self-limiting conditions, easily self-diagnosed and treated by the end consumer.
The proposed classification would allow the consumer to continue to use safe, anthroposophical and homoeopathic OTC medicines that have been available in New Zealand for more than 40 years.

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

Skin inflammations like bee stings, travel sickness, seasickness and jetlag are common, self-limiting conditions, easily self-diagnosed and treated by the end consumer and pharmacist.

3. Relevant comparative data for like compounds

Not applicable

4. Local data or special considerations relating to NZ

None known.

5. Interactions with other medicines

None known.

6. Contraindications

None known.

7. Possible development of drug resistance

None known.

8. Adverse events

Weleda medicines containing Belladonna and Hyoscyamus have been available in New Zealand for over 40 years and in Germany for over 80 years.
During these years there have been, to our knowledge, no reports of any adverse events associated with these medicines.

9. Potential for abuse or misuse

We have no information that could indicate that there is any potential for abuse or misuse.

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: Copies of draft labels for Belladonna 3x and Belladonna 4x.

Reference Copies

1. Reference Copy 1: Belladonna herb and root, pg. 354- 357, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
2. Reference Copy 2: Belladonna Tincture, pg. 1018, British Pharmacopoeia 1988, Volume II, ISBN 0 11 320837 5
3. Reference Copy 3: Atropa belladonna and Hyoscyamus niger, 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
4. Reference Copy 4: Atropa monograph, pg. 36, 37 British Herbal Pharmacopoeia 1983, published by the British Herbal Medicine Association, ISBN 0 903032 07 4
5. Reference Copy 5: Belladonna monograph, pg. 87, 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: Belladonna Herb and Root, pg. 420-421, Martindale, 30th Ed. ., published by The Pharmaceutical Press, ISBN 0 85369 300 5, ISSN 0263-5364
7. Reference Copy 7: Belladonna monograph, pg. 207, 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: Hyoscyamus Leaf, pg. 351-353, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
9. Reference Copy 9: Henbane Leaf monograph, 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
10. Reference Copy 10: Hyoscyamine, pg. 427, Martindale, 30th Ed., published by The Pharmaceutical Press, ISBN 0 85369 300 5, ISSN 0263-5364
11. Reference Copy 11: Hyoscyamus monograph, 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
12. Reference Copy 12: *pg. 345, Handbook of Poisoning, 12th Edition*
13. Reference Copy 13: *pg. 1259 Medical Toxicology, Diagnosis and Treatment of Human Poisoning (1988), by Matthew J. Ellenhorn and Donald G. Barceloux*