参考資料９

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

46th Meeting
21-23 February 2006

Schedule 5 – New entry

CHLORHEXIDINE in preparations containing 3 per cent or less of chlorhexidine **except**:

(a) in preparations containing 1 per cent or less of chlorhexidine; or

(b) when in solid preparations.

Appendix B – Amendment

CHLORHEXIDINE – delete entry.

5. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

5.1 SUSDP, PART 4

5.1.1 CYSTEAMINE HYDROCHLORIDE

PURPOSE

The Committee considered the scheduling of cysteamine hydrochloride.

BACKGROUND

Cysteamine hydrochloride is a salt derivative of cysteamine. Cysteamine has been used therapeutically for the management of nephropathic cystinosis in children and adults. Cystinosis is an inherited defect of lysosome transport of cystine. Cysteamine hydrochloride has also been used as an ingredient in cosmetic products as a hair-waving and straightening agent, and as a reducing agent.

At the August 1997 NDPSC Meeting the Committee agreed to include cysteamine in Schedule 4. The Members noted that the PI identified somnolence as an adverse effect and therefore also agreed to an Appendix K entry for cysteamine.

The conversion ratio from cysteamine hydrochloride to freebase cysteamine is ~1.47:1. Thus 7.5% cysteamine hydrochloride is ~5.1% cysteamine. 6% cysteamine would be equivalent to 8.8% cysteamine hydrochloride.

DISCUSSION

The Committee considered a submission XXXXXXXX requesting an exemption to the cysteamine Schedule 4 entry for topical cosmetic use.

The Members noted that XXXXXXXX wished to introduce cysteamine hydrochloride as a replacement for XXXXXXXX in a XXXXXXXX. [Sentence deleted] The pH of the product formulations ranges from approximately 11.7 to 12.4. It was asserted that currently XXXXXXXX products containing XXXXXXXX have a higher pH (approximately 12.6 to 13.2).

The Committee considered a XXXXXXXX evaluation of the XXXXXXXX submission. The evaluation report particularly noted:

- [Paragraph deleted]
- There have been a number of adverse reactions from therapeutic use of cysteamine.
- According to the MIMS Annual 2005, the most common adverse reactions from the therapeutic use of XXXXXXXX containing cysteamine bitartrate (50 or 150 mg) were vomiting, anorexia, fever, diarrhoea, lethargy and rash.
- Adverse reactions involving the gastrointestinal and central nervous systems were especially prominent at the initiation of cysteamine therapy. Central nervous system symptoms included seizures, lethargy, somnolence, depression, and encephalopathy. Gastrointestinal tract symptoms included nausea, vomiting, anorexia, and abdominal pain, sometimes severe. In addition, gastrointestinal ulceration and bleeding had been reported in patients on cysteamine bitartrate therapy.
- A cysteamine dose of 1.95 g/m^2/day (approximately 80 to 90 mg/kg/day) was associated with an increased number of withdrawals from treatment due to intolerance and an increased incidence of adverse effects (vomiting, lethargy, fever).
- Post-marketing reports included one report of interstitial nephritis with early renal failure. A causal relationship between this event and cysteamine bitartrate therapy has not been established. Cysteamine had occasionally been associated with reversible leucopenia and abnormal liver function studies.
- Dermal exposure would be the sole route of human exposure to XXXXXXXX. It was anticipated that the primary consumer would be women, who may use the product on XXXXXXXX. However, male consumers may also use the product to XXXXXXXX.
- Estimated dermal exposures from use of XXXXXXXX cysteamine formulations (10 minutes per event once every two weeks) was provided. The maximum systemic exposure per day was 0.12 mg/kg/day based on the estimated dermal exposure.
- Oral exposure would occur only in the event of accidental ingestion. If a 20 kg child ingested one teaspoon (~5-10 g) of a product containing XXXXXXXX cysteamine exposure would be 37.5 mg/kg. This exposure was roughly equivalent to the daily doses given for the treatment of nephropathic cystinosis, 30 to 75 mg/kg/day. The product package warning advised the consumer to keep product out of reach of children.

- Ocular exposure would only occur with accidental contact with eyes. The XXXXXXXX formulations containing cysteamine have high pH, and irritant properties are predicted. The product package warning advises the consumer to avoid contact with the eyes.

The Committee particularly noted the following points from the evaluation report's assessment of the toxicity information supplied in the submission:

- Cysteamine had low acute oral toxicity (LD_{50} 1352 mg/kg in mice). There was no dermal toxicity data.
- Cysteamine hydrochloride up to 7.5% (approximately 5.11% cysteamine) caused mild skin irritation. [Section deleted]
- Cysteamine hydrochloride showed no evidence of sensitisation XXXXXXXX concentrations of 7.5% and 5% in human patch tests. However, there was a single case report of cysteamine hydrochloride allergic contact dermatitis in a hairdresser. Cysteamine has been used as a reducing agent, typically at concentrations between 5% and 12%, in permanent wave solutions introduced to American beauty salons since 1993.
- At concentrations between 1-10%, cysteamine had caused serious damage to eyes (Members noted advice from the Secretariat that in this instance by "serious" the evaluator meant in the moderate to severe range as per the NDPSC guidelines). Details of the eye toxicity included:
    - [Section deleted] Out of ten eyes receiving 10% eye drops, five showed mild to moderate hyperaemia and thickening of the lower and upper eyelids after 10 days, leading to cessation of this treatment regimen. The eyes receiving 5%, 2% or 1% cysteamine eye drops showed no clinical signs of toxicity, but exhibited a dose dependent infiltration upon histopathological examination. The eyes treated with 0.5% or 0.1% cysteamine showed no clinical or histopathological signs of toxicity. Also, there were no adverse side effects reported in 29 patients exposed to 0.1% and 0.5% cysteamine eye drop in a clinical trial for up to 34 months.
- No robust repeated dose or long term studies in animals with cysteamine were identified.
- In the developmental and reproductive toxicity studies submitted, cysteamine at an oral dose of 375 mg/kg/day (1.5 times the maximum recommended human oral dose, based on body surface area) reduced the fertility of adult rats. The NOAEL for maternal toxicity was 100 mg/kg/day. In another study, the NOAEL for developmental effects was 75 mg/kg/day.
- The genotoxicity profile of cysteamine in vitro was mixed, but it was concluded to be negative in a well conducted in vivo micronucleus study in the mouse bone marrow. Cysteamine had not been tested for carcinogenic potential in long-term animal studies.

The Committee considered the following conclusions from the evaluation report:

- Wide dispersive use with intermittent dermal contact and possibly accidental ocular contact or oral ingestion of cysteamine was expected to occur among public consumers.
- The total daily systemic exposure of an individual was estimated to be 0.12 mg/kg bw/day (based on estimated dermal exposure for a 70 kg person) when used in the proposed XXXXXXXX products at concentrations up to XXXXXXXX cysteamine hydrochloride, or 37.5 mg/kg in the event of accidental ingestion. A cysteamine dose of 1.95 g/m^2/day (approximately 80 to 90 mg/kg/day) had been associated with an increased number of withdrawals from therapeutic treatment of nephropathic cystinosis due to intolerance and an increased incidence of adverse events. In addition, the NOAEL for cysteamine from the reproductive and developmental studies was 75 mg/kg/day. The margin of exposure to cysteamine was therefore estimated to be 625 or 313 under normal use, and in the event of accidental ingestion, respectively. Hence, the risk to the public was likely to be low.

The evaluation report supported the revision of the scheduling for use of cysteamine in topical cosmetic preparations containing 7.5% or less of cysteamine hydrochloride with provision of appropriate warning statements and/or safety directions on the label to reflect its eye irritation and skin sensitising potential. The evaluation report, however, did not recommend a specific schedule for cysteamine hydrochloride when used in cosmetics at a concentration of 7.5% or less. The Members were advised that subsequent discussion with the evaluator by the Secretariat established that the evaluator thought that cysteamine for cosmetic use at these concentrations lay on the border between Schedule 5 and 6 due to the eye irritancy.

The Committee were advised that a pre-meeting comment by XXXXXXXX on the evaluation report provided a reference for the oral LD_{50} study in mice.

The Members also noted that the Martindale Monograph for mercaptamine (the INN for cysteamine hydrochloride), in reference to therapeutic use, which indicated that it may cause gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhoea, and abdominal pain; rarely there may be gastrointestinal ulceration or bleeding. Other adverse effects included drowsiness, malaise, rashes, fever, flushing, and ventricular tachycardia. Mercaptamine may cause increases in liver enzyme values and precipitate hepatic coma in patients with overt hepatic damage. Interstitial nephritis has also occurred rarely. Nervousness, depression, and, rarely, hallucinations, have been reported.

A Member questioned whether there was a need for a warning statement against cosmetic use of cysteamine while pregnant given some evidence of developmental toxicity identified in the evaluation report. The Committee agreed that such a statement was not necessary as the worst-case scenario for female exposure had a safety factor between the estimated exposure and the No Observable Effect Level for developmental toxicity of 94 fold.

Additionally, the Committee decided that there was a need to include safety and first aid directions when for cosmetic use to reflect the eye irritancy potential. However,

Members considered that there was no need to include any such statements for sensitisation as the only concern was a single report of cysteamine induced allergic contact dermatitis in a hairdresser, and the evaluation report had noted no evidence of sensitisation in human patch tests.

Members further noted a submission from XXXXXXXX registering an interest in cysteamine hydrochloride.

DECISION 2006/46 - 13

The Committee agreed:

- That cysteamine hydrochloride for cosmetic use does not warrant capture by Schedule 4 which is for therapeutic use.
- That a new entry in Schedule 6 be included for greater than 6% cysteamine for cosmetic use (equivalent to 8.8% cysteamine hydrochloride) because of severe eye irritancy potential.
- That a new entry in Schedule 5 be include for less than or equal to 6% cysteamine for cosmetic use because of a slight to moderate eye irritancy potential.
- That 1% or less of cysteamine for cosmetic use be exempt from the requirements of scheduling as it presents a very low toxicity or eye irritancy risk.
- To include in the SUSDP the first aid instruction "If in eyes wash out with water" and the safety direction "Avoid contact with eyes" due to the Committee's particular concerns around the eye irritancy potential.

Schedule 4 – Amendment

CYSTEAMINE – amend entry to read:

CYSTEAMINE for human therapeutic use.

Schedule 5 – New entry

CYSTEAMINE in cosmetic preparations containing 6 per cent or less of cysteamine **except** in preparations containing 1 per cent or less of cysteamine.

Schedule 6 – New entry

CYSTEAMINE for cosmetic use **except**:

(a) when included in Schedule 5; or

(b) in preparations containing 1 per cent or less of cysteamine.

Appendix E - Part 2 – New entry

POISON	STANDARD STATEMENTS
Cysteamine	E1

Appendix F - Part 3 – New Entry

Poison	Warning Statement	Safety Directions
Cysteamine		1

5.1.2 SODIUM POLYSTYRENE SULPHONATE

PURPOSE

The Committee considered the scheduling of sodium polystyrene sulphonate (SPS).

BACKGROUND

SPS is the sodium salt of polystyrene sulphonic acid (PSS). The SPS polymer is highly charged with anionic sulphonic acid groups linked to aromatic rings of the polymer backbone. SPS is available in two forms:

- A water-soluble non-cross linked form used as the cosmetic ingredient (trade name XXXXXXXX, an off-white powder consisting of 90% SPS with a molecular weight of approximately 130,000 where a 30% aqueous solution has a pH range of 5.5-8.5.). SPS is used in formulations overseas including hair care (such as hair styling aid, thermal protective products, shampoos and conditioners) and anti-wrinkle skin care products. SPS is also used as emulsion stabilisers, film formers, surfactants and viscosity controlling agents.
- A cross-linked water-insoluble form which is used in current therapeutic applications. SPS is currently the active used in a listed medicine for treatment of hyperkalemia and hyperphosphatemia according to the ARTG. The function of the SPS in this therapeutic product was to treat high blood level potassium by removing potassium from the body by exchanging it with sodium in the gut. SPS is also used as an excipient in four phentermine resin products. The therapeutic uses of SPS are substantially different from the cosmetic use.

At the August and November 1999 NDPSC Meetings the Committee agreed to include SPS in Schedule 4 to harmonise with New Zealand as recommended by the trans-Tasman Harmonisation Working Party.

At the June 2005 NDPSC Meeting the Members considered an application from XXXXXXXX requesting an exemption from Schedule 4 for topical cosmetic use of