**Australian Government**
**Department of Health and Ageing**
**Therapeutic Goods Administration**

# Minute

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Office of Complementary Medicines

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**Re: Listing Notice for Sodium Fluoride**

Please find attached a review of the availability of sodium fluoride as an active ingredient in listed medicines. On the basis of this review, it is identified that the Therapeutic Goods (Listing) Notice 2008 (No. 1) for sodium fluoride has not been updated in line with changes made to the relevant schedules of the Poison Standard. I recommend that the TGA amend the Therapeutic Goods (Listing) Notice 2008 (No. 1) for sodium fluoride to allow **up to 1500 mg/kg** of fluoride in listed medicines with inclusion of relevant advisory statements.

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Pre-market Assessment Section
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# INTRODUCTION

On 25 February 2013, Catherine Oh, Manager of Regulatory & Technical, Accord Australasia wrote to Dr Peter Bird of TGA regarding the fluoride level in toothpaste which was also raised at the TGA/Accord bilateral meeting (f. 1-3, 2013/006971). Catherine stated that:

- The acceptance level of fluoride in toothpastes has changed in the Standard for the Uniform Scheduling of Drug and Poisons (Poison Standard) in 2008 to allow toothpastes containing up to 1500 mg/kg fluoride for both therapeutic and non-therapeutic use to be exempted from scheduling requirements.
- While the Therapeutic Goods (Listing) Notice 2008 (No. 1) gazetted in February 2008 for Sodium Fluoride requires that the concentration of fluoride ion is not more than 1000 mg/kg and the notice has not been updated when this change was made to the Poison Standard (f. 5-7, 2013/006971).

In April 2013, this issue was forwarded to the Office of Complementary Medicines (OCM) and in response Trisha Garrett, the Head OCM, agreed that the TGA will review this ingredient, including all current conditions placed on its use, the scheduling requirements for the substance sodium fluoride and any other relevant information to determine whether there is a need for drafting a new listing notice (f. 4, 2013/006971).

The changes to the fluorides scheduling (in particular Schedules 2, 3 and 4) in the Poison Standard and the Listing Notice are reviewed in this report.

# BACKGROUND

## Scheduling

Prior to June 2004, Schedule 2, 3 and 4 entries for "fluorides' (f. 9-10, 2013/006971) were:

**Schedule 2**

FLUORIDES for human therapeutic use (except in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or
(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion except:
  (i) dentrifices included in Schedule 3;
  (ii) dentrifices containing 1000 mg/kg or less of fluoride ion; or
  (iii) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion.

**Schedule 3**

FLUORIDES in pastes, powders or gels for the cleaning of teeth containing more than 1000 mg/kg of fluoride ion.

**Schedule 4**

FLUORIDES in preparations for human therapeutic use except:

(a) when included in Schedule 2 or 3;

(b) pastes, powders or gels for the cleaning of teeth containing 1000 mg/kg or less of fluoride ion;
(c) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion; or
(d) in other substances containing 15 mg/kg or 15 mg/L or less of fluoride ion.

The 1000 mg/kg Schedule 2(b)(ii) exemption for dentrifices, and the general Schedule 2 exemption for ≤ 15 mg/kg were introduced at the February 1986 DPSSC Meeting. Dentrifices with >1000 mg/kg fluoride ion were included in Schedule 3 at the July 1987 DPSSC Meeting. The 2.5 % cut-off in part (b) of the Schedule 2 entry resulted from a February 2001 National Drugs and Poisons Schedule Committee (NDPSC) decision to harmonise with New Zealand.

The February 2004 NDPSC Meeting agreed to exempt dental hygiene products which were not dentrifices (such as mouth rinses) containing ≤ 220 mg/kg fluoride ion, conditional upon a 120 mg pack size, child-resistant closure (CRC) and label warnings against swallowing the product and use in children under six. Other preparations were included in Schedule 2 or exempted from scheduling. The June 2004 NDPSC Meeting varied this decision by replacing "for human therapeutic use" in the fluoride entries with "for human use". No Committee discussion was minuted regarding those non-therapeutic products for human use which were now captured e.g. fluoride containing dental whiteners (f. 18-19, 2013/006971).

The Committee considered some minor changes to the Schedule 2 and Schedule 4 entries at the February, June and October 2005 NDPSC Meetings as a consequence of the introduction of the *Required Advisory Statements for Medicines Labels* (RASML).

In the June 2006 NDPSC Meeting (f. 31-42, 2013/006971), the committee was advised by a member that it appeared that the June 2004 amendment to the Schedule 2 fluorides entry had a wider regulatory impact than intended. Members agreed to gazette consideration of this issue at the October 2006 NDPSC Meeting.

The October 2006 NDPSC Meeting (f. 43-53, 2013/006971):

- Agreed that pastes, powders or gels containing 15 mg/kg < fluoride ion ≤ 1000 mg/kg for all applications to teeth (including dental hygiene, whitening and bleaching) did not warrant scheduling as there was little risk of these formulations being ingested in sufficient quantities to cause harm. Members therefore agreed to amend Schedule 2(b)(ii), Schedule 4(b), Schedule 5(b) and Schedule 6(b) by replacing the current wording with "dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion".
- Confirmed that it was appropriate that all pastes, powders or gels for use on teeth containing > 1000 mg/kg fluoride be controlled by the Schedule 3 entry as the risks from this concentration of fluoride ion required pharmacist advice. Members therefore agreed to amend Schedule 3 by replacing the current wording with "dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing more than 1000 mg/kg of fluoride ion".
- Agreed that other formulation types (i.e. not pastes, powders or gels) for topical oral use containing 220 mg/kg < fluoride ion ≤ 2.5% (including dental hygiene and whitening) were to be Schedule 2 due to the increased risk of such formulations being ingested in a quantity which may cause harm.
- Agreed that the public health risks of topical dental hygiene, whitening or bleaching products containing 15 mg/kg < fluoride ion ≤ 220 mg/kg (except as specified by (b)(ii) in the Schedule 2 fluorides entry) would be acceptably minimised through labelling, pack size

limitations and a CRC requirement. Where these conditions were not met, capture by Schedule 2 was appropriate. Members therefore agreed to amend Schedule 2(b)(iii) and (iv), Schedule 4(c) and (d), Schedule 5 (c) and (d) and Schedule 6 (c) and (d) to allow dental whiteners and bleachers to qualify for these exemptions by adding ", whitening or bleaching" after the existing "other dental hygiene".

The schedules for fluorides were subsequently amended to:

**Schedule 2**

FLUORIDES for human use (except in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or
(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion except:
  (i) when included in Schedule 3;
  (ii) dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion;
  (iii) other dental hygiene, whitening or bleaching products that are therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or
  (iv) other dental hygiene, whitening or bleaching products that are not therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:
    (A) Do not swallow; and
    (B) Do not use [this product/name of product] in children six years of age or less.

**Schedule 3**

FLUORIDES in dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing more than 1000 mg/kg of fluoride ion.

**Schedule 4**

FLUORIDES in preparations for human use except:

(a) when included in Schedule 2 or 3;
(b) dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion;
(c) other dental hygiene, whitening or bleaching products that are therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;
(d) other dental hygiene, whitening or bleaching products that are not therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:
  (i) Do not swallow; and
  (ii) Do not use [this product/name of product] in children six years of age or less; or
(e) other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

The February 2007 NDPSC Meeting noted some issues regarding the fluoride scheduling. The June 2007 NDPSC Meeting subsequently established a Fluorides Working Party (FWP) to review the fluoride scheduling framework (f. 54-67, 2013/006971). The October 2007 NDPSC Meeting noted the FWP progress, including a number of proposals that the Committee agreed should be considered at the February 2008 NDPSC Meeting.

In February 2008, the Committee considered the scheduling of fluorides for human use, including specific proposals from the October 2007 NDPSC Meeting (f. 68-93, 2013/006971).

The Committee decided:

**General**

- To confirm that Schedule 4 was the fluoride parent entry for all human use.
- To confirm the ≤ 15 mg/kg fluoride ion general exemption from scheduling.

**Ingestion**

- To reduce the Schedule 4 to Schedule 2 cut-off for preparations for ingestion (i.e. fluoride supplements) to ≤ 0.5 mg fluoride ion per dosage unit.

**Liquid**

- To capture liquid preparations for topical use in Schedule 4 unless:
  - ≤ 220 mg/kg, in packs containing ≤ 120 mg total fluoride when fitted with a child-resistant closure (CRC) and labelled:
    - according to the RASML when for therapeutic use; or
    - with warning statements to the effect of "Do not swallow" and "Do not use in children 6 years of age or less" when for non therapeutic use

    which will be exempt from scheduling.
  - ≤ 1000 mg/kg, fitted with a CRC and labelled as above, which will be Schedule 2 unless exempted above.
  - ≤ 5500 mg/kg, fitted with a CRC, which will be Schedule 3 unless exempted above or captured by Schedule 2.

**Non-liquid**

- To capture non-liquid preparations for topical use in Schedule 4 unless:
  - ≤ 1000 mg/kg, which will be exempt from scheduling;
  - > 1000 mg/kg and ≤ 1500 mg/kg, which will also be exempt when labelled:
    - according to the RASML when for therapeutic use; or
    - with warning statements to the effect of "Do not swallow" and "Do not use in children 6 years of age or less" when not in a therapeutic product.
  - ≤ 5500 mg/kg, which will be Schedule 3 unless exempted above.

The Committee also decided to simplify the various schedule entries (including use of the expression "when included in or expressly excluded from") as listed below.

**Schedule 2 - Amendment**

FLUORIDES – Amend entry to read:

FLUORIDES for human use:

(a) in preparations for ingestion containing 0.5 mg or less of fluoride ion per dosage unit; or

(b) in liquid preparations for topical use containing 1000 mg/kg or less of fluoride ion, in a container with a child-resistant closure:

(i) for therapeutic use when compliant with the requirements of the *Required Advisory Statements for Medicine Labels* except in preparations containing 220 mg/kg or less of fluoride ion, in packs containing not more than 120 mg total fluoride when fitted with a child-resistant closure and compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or

(ii) for non-therapeutic use when labelled with warnings to the following effect:
   (A) Do not swallow; and
   (B) Do not use [this product/name of product] in children six years of age or less,

except in preparations containing 220 mg/kg or less of fluoride ion, in packs containing not more than 120 mg total fluoride, when fitted with a child-resistant closure and labelled with warnings to the following effect:
   (A) Do not swallow; and
   (B) Do not use [this product/name of product] in children six years of age or less,

except in preparations containing 15 mg/kg or less of fluoride ion.

**Schedule 3 - Amendment**
FLUORIDES – Amend entry to read:

FLUORIDES for **human topical use**:

(a) in liquid preparations containing 5500 mg/kg or less of fluoride ion, in a container with a child-resistant closure except when included in or expressly excluded from Schedule 2; or

(b) in non-liquid preparations containing 5500 mg/kg or less of fluoride ion except:
   (i) in preparations for therapeutic use containing 1500 mg/kg or less of fluoride ion and, when containing more than 1000 mg/kg fluoride ion, compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or
   (ii) in preparations for non-therapeutic use containing 1500 mg/kg or less of fluoride ion and, when containing more than 1000 mg/kg fluoride ion, labelled with warnings to the following effect:
      (A) Do not swallow; and
      (B) Do not use [this product/name of product] in children six years of age or less.
   (iii) in preparations for supply to registered dental professionals or by approval of an appropriate authority.

**Schedule 4 - Amendment**
FLUORIDES – Amend entry to read:

FLUORIDES in preparations for human use except when included in or expressly excluded from Schedule 2 or 3.

The above amendment came into effect in June 2012 and is current in the Poison Standard.

This increase in the amount of fluoride permitted at general sale level should affect only mouthwashes. Classification levels for all other products containing fluoride should remain unchanged.

During this review, it was noted that both the current RASML and the proposed revision (Update 6) do not link the required advisory statements for fluoride (statements 122 and 150) to the entry for sodium fluoride. Analogous entries, such as those for 'Silver' and 'Silver salts' include notes

relating the ingredients. It has been suggested to staff responsible for the RASML that similar links are included in Update 6, e.g. the entry for sodium fluoride be annotated '*See also fluoride*'.

## Therapeutic Goods (Listing) Notice

In August 2007, the Safety Assessment Unit, OTCMS, NPM Branch of TGA performed a safety review on the use of sodium fluoride as an active ingredient in pharmaceutical products (f. 108, 2013/006971, attached in this report). The TGA safety review did not reveal any safety concern for sodium fluoride to allow up to **1450 ppm** fluoride ion as stated in the report that:

> "Internationally, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) approved Colgate Whitening Toothpaste containing sodium fluoride 0.32% (**1450 ppm**) for general sale".

Subsequently, Dr Peter Bird wrote a minute to Michael Wiseman, manager of Listing Section, OCM (f. 109, 2013/006971) and recommended that sodium fluoride be allowed for use as an active ingredient in listed medicines that:

- the preparation includes at least one other therapeutically active Listable ingredient;
- the concentration of the fluoride ion is not more than 1000 mg/kg (1000 ppm);
- the substance is for use only in pastes, powders or gels for the cleaning of teeth;
- claims in relation to fluoride content are restricted to those relating to improvements in oral hygiene or use of fluoride for the prevention of tooth decay.

It therefore appears that the concentration limit applied to the fluoride ion was set in accordance with the Poisons Standard and not due to an inherent safety concern.

In a Minute of New Complementary Medicine Substances for use in listable goods, David Briggs, Director, Office of Complementary Medicines wrote to the National Manager seeking approval of new substance, sodium fluoride, for use in Listed Medicines (f. 110-112, 2013/006971), in which it stated that:

(A) Sodium fluoride is the subject of monograph of the *British Pharmacopoeia* and its safety profile is well established in this application.
(B) Sodium fluoride is a source of fluoride that is widely used in toothpaste products at concentrations of fluoride ion of up to 1000 mg/kg without evidence of safety concerns. A safety review by the Non-Prescription Medicines Branch did not reveal any safety concerns with this source of fluoride that would preclude the use of this substance in Listed medicines provided that:
    - the concentration of the fluoride ion is **not more than 1000 mg/kg**;
    - the substance is for use only in pastes, powders or gels for the cleaning of teeth; and
    - claims in relation to fluoride content are restricted to those relating to improvements in oral hygiene or the use of fluoride for the prevention of tooth decay.

The Minute also noted:

> "Fluorides" are listed in Schedules 2, 3 and 4 of the *Standard for the Uniform Scheduling of Drugs and Poisons* (Poison Standard). However, the Poison Standard excludes from scheduling fluorides in dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, **containing 1000 mg/kg or less of fluoride ion**. Products for different purposes, in different forms, or with a higher concentration of fluoride ion are

not excluded from scheduling and would therefore be ineligible for Listing on the Australian Register of Therapeutic Goods.

Subsequently, a minute advertising Senator McLucas of the new listable substance has been signed by the then National Manager, Dr Rohan Hammett (f. 113-115, 2013/006971).

The Regulatory Practice Committee (RPC) of the TGA considered the proposed listing at its meeting of 13 November 2007 (f. 116-119, 2013/006971).

On the 4th February 2008, the Therapeutic Goods (Listing) Notice signed by Dr Rohan Hammett (the National Manager) that permits use of sodium fluoride under certain conditions was published on the Federal Register of Legislative Instruments (f. 7, 2013/006971). The delegate of the Minister for Health and Ageing for the purposes of subsection 9A(5) of the Therapeutic Goods Act 1989 (the Act) and acting under that provision, requires the following therapeutic goods to be included in the part of the Australian Register of Therapeutic Goods (ARTG) for listed goods:

- preparations, referred to in Item 3, Part 1 of Schedule 4 of the *Therapeutic Goods Regulations 1990*, for oral use that contain, in combination with at least one other therapeutically active ingredient referred to in Item 3, sodium fluoride, being a substance that is to be mentioned in Part 3 of Schedule 4 of the *Therapeutic Goods Regulations 1990*, and which comply with the following requirements:
  - the concentration of fluoride is not more than 1000 mg/kg; and
  - the substance is for use only in pastes, powders or gels for dental hygiene; and
  - claims in relation to fluoride content are restricted to those relating to improvements in dental hygiene or the use of fluoride for the prevention of tooth decay.

The above conditions on the use of sodium fluoride in listed medicines are consistent with the currently applied validation rules within the Electronic Listing Facility.

## RECOMMENDATION

The current scheduling of fluoride exempts therapeutic dental preparations such as pastes, powder or gels containing 1500 mg/kg or less fluoride ion from scheduling, while listed medicines may only contain up to 1000 mg fluoride /kg.

It is recommended that the OCM review the Listing Notice for sodium fluoride to allow up to 1500 mg fluoride /kg in listed medicines.

Dr Xiangting Zhou
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Office of Complementary Medicines

11 June 2013

SODIUM FLUORIDE
ACTIVE IN LISTED ME