Submission for Vitamin A

Part A
1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Retinol (Vitamin A) - includes retinol acetate [synonym retinol acetate], retinol palmitate [synonym retinyl palmitate], retinol propionate.

2. Proprietary name(s).

Not applicable.

3. Name of the company / organisation / individual requesting a reclassification.

Not applicable. This request is made on behalf of the natural health products industry.

4. Dose form(s) and strength(s) for which a change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

5. Pack size and other qualifications.

Not applicable. This request is made on behalf of the natural health products industry.

6. Indications for which change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

7. Present classification of the medicine.

At the present time, Vitamin A is:

- Unscheduled when in products for external use containing 1 percent or less.
- Unscheduled when in products for internal use containing 3 milligrams or less of retinol equivalents per recommended daily dose [ie 10,000 IU].
- Unscheduled when in parenteral nutrition replacement preparations.
- A prescription medicine except in the situations above.

8. Classification sought.

It is proposed that the classification of Vitamin A is changed to:

- Unscheduled when in products for external use containing 1 percent or less.
- Unscheduled when in products for internal use containing 6 milligrams or less of retinol equivalents or less per recommended daily dose [ie 20,000 IU].
- Unscheduled when in parenteral nutrition replacement preparations.
- A prescription medicine except in the situations above.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Australia
Vitamin A is:

- Unscheduled when in products for topical use containing 1 per cent or less of Vitamin A.
- Unscheduled when in products for internal use containing less 3000 micrograms retinol equivalents or less of Vitamin A per recommended daily dose [ie 10,000 IU].
- Unscheduled when in parenteral nutrition replacement preparations.
- A prescription medicine except in the situations above.

Canada
Vitamin A is:

- Unscheduled in oral dosage form containing 10,000 International Units [ie 3 mg] of Vitamin A per dosage form or less, or where the largest recommended daily dosage shown on the label would, if consumed by a person, result in the daily intake by the person of less than 10,000 International Units of Vitamin A.
- Prescription drug in oral dosage form containing more than 10,000 International Units [ie 3 mg] of Vitamin A per dosage form or, where the largest recommended daily dosage shown on the label would, if consumed by a person, result in the daily intake by the person of more than 10,000 International Units of Vitamin A.

UK
Vitamin A is:

- Unscheduled in products for internal use containing 7,500 IU or less of Vitamin A (ie 2,250 µg or 2.25 mg retinol equivalent).
- A pharmacy medicine if in products for external use.
- A prescription medicine except in the situations above.

USA
In the USA, many vitamin A products are marketed as dietary supplements which do not have to undergo a pre-approval process. There are at least 5,600 products containing Vitamin A on the USA market. The vitamin content of these products ranges from 5,000 IU to 25,000 IU [or 1.5 mg to 7.5 mg].

10. Extent of usage in New Zealand and elsewhere (eg sales volumes) and dates of original consent to distribute.

No information was provided by the applicant. However, there are a number of multi-vitamin and mineral supplements on the market, all not exceeding a maximum daily dose of 3 mg retinol equivalents.

11. Labelling or draft labelling for the proposed new presentation(s).

Not applicable. Presumably the labels will be the same as those in Appendix 1.

12. Proposed warning statements if applicable.

When used as an active ingredient in oral or sublingual products:

Vitamins can only be of assistance if the dietary vitamin intake is inadequate [OR] Vitamin supplements should not replace a balanced diet.

When the dose contains between 100 IU (30.3 micrograms retinol equivalents) and the MDD:

The recommended adult daily amount of vitamin A from all sources is 2500 IU (750 micrograms retinol equivalents).
Do not use without consulting a doctor or pharmacist if pregnant or intending to become pregnant, or breastfeeding.

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

Manufacturers of current dietary supplement-type products will likely increase the quantity of Vitamin A in their products, or change their dosing instructions to deliver the maximum dose.

It should be noted that all dietary supplement products will be regulated under the NHP Bill. When the NHP Bill is passed, natural health products will have to be manufactured according to a Code of Manufacturing Practice.

<u>Approved medicines containing Vitamin A as the active ingredient</u>

- Vitalipid N Adult emulsion for injection
- Vitalipid N Infant emulsion for injection
- Cernevit powder for injection
- Vit-a-Pos eye ointment

Products for injection and for application to the eye are not permitted to be natural health products.

- ReTrieve topical cream — prescription medicine
- Ungvita topical cream — general sale

Topical creams are not affected by the requested change for an increase in the daily dose for internal use.

- Vesanoid capsules — prescription medicine

Vesanoid capsules contains 10 mg tretinoin (retinoic acid). This medicine will not be affected by the requested change.

Part B Reasons for requesting classification change including benefit-risk analysis.

Vitamin A was last considered by the Medicines Classification Committee at the 37th Meeting, 17 May 2007.

The minutes from the 37th Meeting are reproduced here.

The NDPSC recommended that New Zealand should adopt a schedule entry which would allow topical preparations containing 1 percent or less of vitamin A to be general sale medicines. Topical preparations containing more than 1 percent were prescription medicines in Australia. The New Zealand schedule did not currently make provision for topical products.

It was noted that there were two current topical prescription medicines products on the New Zealand database which contained 0.05 percent vitamin A acid. These were covered under the prescription medicine entry for tretinoin which is the rINN for vitamin A acid.

The Committee agreed that an exemption from the prescription medicine status of vitamin A should be added to the current prescription medicine entry to allow topical products to be general sale medicines when in products containing 1 percent or less. It was also agreed that the current prescription medicine entry should be amended to refer only to products for oral use.

Recommendation

That vitamin A should be classified as a prescription medicine when:

- *for oral use in medicines containing more than 3000 micrograms of retinol equivalents per recommended daily dose except in parenteral nutrition replacement preparations*
- *for external use except in medicines containing 1% or less.*

Prior to this the MCC considered Vitamin A at the 24th Meeting, 2 November 2000, as part of the process to harmonise the medicines schedule with Australia. The minutes from this meeting consists only of two recommendations:

- *That the prescription medicine entry for retinol be deleted from the schedule.*
- *That the prescription medicine entry for vitamin A be amended to:*
  "in preparations containing more than 3000mcg retinol equivalents per recommended daily dose."

This section should be supported by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change.

No information was provided by the applicant in relation to benefits to the consumer or to the public from doubling the recommended dose of Vitamin A.

Multi-ingredient supplements such as trace elements and essential nutrient formulations are usually taken to complement dietary intake of essential vitamins and minerals. Such products are generally regarded as dietary supplements.

At the present time, under the current Dietary Supplements Regulations regime, therapeutic claims are not permitted for dietary supplements. This creates a peculiar situation where, for

example, iron supplements are recognised to aid in the treatment of iron deficiency and iron deficiency anaemia, and are taken for these purposes, yet such products cannot provide advice on their labels on how they should be used. The NHP Bill is intended to address this situation.

When the NHP Act comes into effect, certain health benefits will be able to be claimed for allowed health conditions, provided the manufacturer of the natural health product holds evidence to support the claim(s) being made. For example, iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill. Similarly, a claim for treatment of acne, or boosting the immune system with vitamin A could be allowed.

The clear benefit of allowing the requested change is that it will enable easier implementation of the NHP system by allowing the essential vitamin or mineral to be present in effective quantities or in effective doses in natural health products.

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

The Ministry of Health's recommendations for Vitamin A (MOH, 2006) are presented in the following table:

Age group and gender		Vitamin A (retinol equivalents) µg / day		
		AI		UL
Infants	0-6 months	250		600
	7-12 months	430		600
		EAR	RDI	UL
Children	1-3 years	210	300	600
	4-8 years	275	400	900
Boys	9-13 years	445	600	1,700
	14-18 years	630	900	2,800
Girls	9-13 years	420	600	1,700
	14-18 years	485	700	2,800
Men	19-30 years	625	900	3,000
	31-50 years	625	900	3,000
	51-70 years	625	900	3,000
	> 70 years	625	900	3,000
Women	19-30 years	500	700	3,000
	31-50 years	500	700	3,000
	51-70 years	500	700	3,000
	> 70 years	500	700	3,000
Pregnancy	14-18 years	530	700	2,800
	19-30 years	550	800	3,000
	31-50 years	550	800	3,000
Lactation	14-18 years	780	1,100	2,800
	19-30 years	800	1,100	3,000
	31-50 years	800	1,100	3,000

AI adequate intake
EAR estimated average requirement
RDI recommended daily intake
UL upper level of intake

Toxicity information

Too much vitamin A in retinoid form can be harmful or fatal, resulting in what is known as hypervitaminosis A. In humans, where expressed feelings of pain or illness on the part of the patient provide an early indication of adverse effects, the symptoms and signs of hypervitaminosis A vary in severity with the dose level, and include skin dryness, anorexia, headache, weakness, hair loss, joint pain, vomiting, irritability, enlarged liver and spleen, and bulging fontanel and increased intracranial pressure in babies.

The lowest reported adverse effect level in humans appears to lie in the range 700 to 1,000 IU per kg per day, if continued for periods of several months (SCOG, 1980). This would equate to about 14 mg/day for a 70 kg person). Many studies have demonstrated that the use of high doses of vitamin A of up to 300,000 IU (90 mg/day) for a few months (to treat various ailments) does not cause toxicity (Balch and Balch, 1999; Segala, 2000). The risk of vitamin A toxicity increases if high doses are used for longer than a few months. Osiecki (2014) considers that toxicity occurs at doses above 75 mg/day.

The following table lists the daily doses of Vitamin A recommended from a variety of sources/researchers:

Dosage	Retinol equivalents	Reference
2,500 IU	0.75 mg	Mervyn, L. Thorsons. Complete Guide to Vitamins and Minerals (2nd Edition). Thorsons Publishing Group, Wellingborough, England. 1989:18.Minimum recommended dosage. Murray, Michael T. The Encyclopedia of Nutritional Supplements: the essential guide for improving your health naturally. Prima Publishing, Rocklin, California, USA. 1996:36.Dosage for minimum health maintenance for women.
5,000 IU	1.5 mg	Murray, Michael T. The Encyclopedia of Nutritional Supplements: the essential guide for improving your health naturally. Prima Publishing, Rocklin, California, USA. 1996:36. Dosage for minimum health maintenance for men.
7,500 IU	2.25 mg	Mervyn, L. Thorsons Complete Guide to Vitamins and Minerals (2nd Edition). Thorsons Publishing Group, Wellingborough, England. 1989:18. The author believes that supplemental vitamin A should not exceed this dosage.
15,000 IU	4.5 mg	Balch, J. F. & Balch, P. A. Prescription for Nutritional Healing (2nd Edition). Avery Publishing Group. 1997:346-347.Dosage recommended for the treatment of influenza on the basis of the known ability of vitamin A to enhance immunity.
25,000 IU	7.5 mg	Jafarirad, S., et al. The effect of vitamin A supplementation on stimulated T-cell proliferation with myelin oligodendrocyte glycoprotein in patients with multiple sclerosis. J Neurosci Rural Pract. 3(3):294-298, 2012. Dosage used in clinical study that demonstrated benefits in multiple sclerosis patients.
30,000 IU	9 mg	Hartmann, S., et al. Exposure to retinyl esters, retinol, and retinoic acids in non-pregnant women following increasing single and repeated oral doses of vitamin A. Ann Nutr Metab. 49(3):155-164, 2005. Daily dosage used to test for toxicity. No toxicity was found using this dosage on a daily basis for 21 days.

50,000 IU	15 mg	Murray, Michael T. The Encyclopedia of Nutritional Supplements: the essential guide for improving your health naturally. Prima Publishing, Rocklin, California, USA. 1996:36. Dosage taken for one to two days for the treatment of acute viral infections.
100,000 IU	30 mg	Balch, J. F. & Balch, P. A. Prescription for Nutritional Healing (2nd Edition). Avery Publishing Group. 1997:428-429.Dosage recommended for the treatment of pneumonia. This high dose of vitamin A should be administered in the form of liquid emulsion. Segala, M. (editor). Disease Prevention and Treatment 3rd Edition. Life Extension Media. Florida, USA. 2000:139.Dosage (of water-soluble vitamin A liquid) for cancer patients (lower end of range).
300,000 IU	90 mg	Segala, M. (editor). Disease Prevention and Treatment 3rd Edition. Life Extension Media. Florida, USA. 2000:139. Dosage (of water-soluble vitamin A liquid) for cancer patients (upper end of range).

Hypervitaminosis A

The risk for developing hypervitaminosis A is related to total cumulative dose of vitamin A rather than a specific daily dose (Kowalski et al, 1994; Meyers et al, 1996). Health Canada recommends the following in order to mitigate the risk of hypervitaminosis A:

In products containing both vitamin A and beta-carotene, the risk of hypervitaminosis A is to be mitigated by ensuring that the combined doses of these two medicinal ingredients is not excessively high. Therefore, the combined dose of vitamin A plus beta-carotene must not exceed the maximum dosage value for vitamin A, measured in µg Retinol Activity Equivalent (RAE). The conversion factor of 6 µg beta-carotene = 1 µg RAE (HC 1990; FAO/WHO 1967) can be applied for the specific purpose of ensuring safety of the combined dose. The example below illustrates how the 6:1 conversion factor can be used to determine the safety of combinations including beta-carotene and vitamin A:

Example:

The maximum dosage value of vitamin A for adults is 3000 µg RAE per day. If a product contained 2800 µg vitamin A (i.e. all-trans retinol, vitamin A acetate, vitamin A palmitate), then it could contain no more than 1200 µg beta-carotene. See calculation below:

2800 µg vitamin A + 1200 µg beta-carotene (200 µg RAE) = 3000 µg RAE.

Note: The value of 3000 µg RAE is to demonstrate the safety of the combination of vitamin A and beta-carotene only and must not appear on the PLA form or label.

Osteoporosis

Vitamin A can increase the risk for osteoporosis. Chronic, high intake of vitamin A 10,000 IU or more per day seems to increase the risk of osteoporosis and hip fracture in postmenopausal women (Feskanich et al, 2002; Melhus et al, 1998) and overall risk of fracture in middle-aged men (9190). High serum retinol levels also increase the risk of fracture in men. Men with high serum retinol levels are seven times more likely to fracture a hip than men with lower serum retinol levels (Michaelsson et al, 2003). Vitamin A damage to bone can occur subclinically, without signs or symptoms of hypervitaminosis A. Older people have higher levels of vitamin A and might be at increased risk for vitamin A-induced osteoporosis. The practice of fortifying foods such as margarine and low-fat dairy products vitamin A has led to concern that consumption of these foods in addition to vitamin A or multivitamin supplements may cause excessive serum retinol levels.

Pregnancy and Teratogenicity

Excess preformed vitamin A during early pregnancy has also been associated with a significant increase in birth defects (Challem, 1995). These defects may be severe, even life-threatening. Even twice the daily recommended amount can cause severe birth defects (Stone, 1995).

Hartman et al (2005) examined the exposure of non-pregnant women to retinyl esters, retinol and retinoic acid. The authors evaluated plasma concentration-time curves of retinyl esters, retinol and their metabolites at increasing doses of vitamin A. This was an open-label dose-response study. Non-pregnant females (3 groups with n = 12; 18-40 years) received once daily oral doses of vitamin A palmitate up to 30,000 IU/day over 21 days. The area under the plasma concentration-time curve ($AUC_{(24h)}$) served as indicator for exposure. $AUC_{(24h)}$ of retinyl esters increased linearly with dose. Retinol concentrations were unaffected. All-trans RA exhibited a diurnal-like concentration-time profile ($C_{(max)}$ at 3 h; $C_{(min)}$ at 8 h), concentrations decreasing below pre-dose levels at 5 h and regaining pre-dose levels at 16 hours. The maximum temporary increase in exposure was 33 percent (single dose) and 19 percent (repeated doses) above baseline, but $AUC_{(24h)}$ remained unaltered. $AUC_{(24h)}$ increased linearly with dose for 13-cis RA and 13-cis-4-oxo RA. Repeated doses caused a 25 percent increase in exposure with the highest vitamin A intake. Accumulation of 13-cis- 4-oxo RA at 30,000 IU/day doubled compared to the 4,000 IU/day intake. Repeated oral doses of up to 30,000 IU of vitamin A in addition to dietary vitamin A were without safety concern. Hartman et al (2005) suggested that safe doses are probably higher, since plasma concentrations and exposure to RA remained at levels earlier shown to be without increased risk of teratogenicity in pregnant women

The NHS considers that although vitamin A is necessary for foetal development, most women carry stores of vitamin A in their fat cells, so over-supplementation should be strictly avoided. The UK Department of Health advises that sufficient vitamin A can be obtained by eating a varied and balanced diet. Their advice is that women who are pregnant or are thinking of having a baby should not take supplements containing Vitamin A unless advised by a practitioner, and should not eat products that are high in vitamin A content, such as liver (NHS, 2015).

Other considerations

Myhre et al (2003) performed a meta-analysis of case reports on toxicity claimed to be induced by intakes of excessive amounts of dietary retinol (ie, retinol and retinyl esters in foods or supplements). They concluded that doses as low as 0.2 mg retinol/kg/day in water-miscible, emulsified, and solid preparations for only a few weeks caused chronic hypervitaminosis A, compared to daily doses of 2 mg retinol/kg in oil-based preparations for many months or years (Myhre et al, 2003). Their analysis indicated that water-miscible, emulsified, and solid preparations of retinol were approximately 10 times as toxic as are oil-based retinol preparations. The safe upper single dose of retinol in oil or liver seems to be approximately 4-6 mg/kg body wt (12,000 – 18,000 IU per kg of body weight). These thresholds do not vary considerably with age. The results of the analysis indicate that the physical form of retinol supplements is a major determinant of toxicity. The use of water-miscible, emulsified, and solid preparations of retinol should be considered before being used in supplements and fortifications.

The data indicate that high doses of Vitamin A for treatment of various ailments for up to a few months does not cause toxicity.

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.

Not applicable.

4. Relevant comparative data for like compounds.

Not applicable.

5. Local data or special considerations relating to New Zealand.

At this time the Medicines Schedule entry for Vitamin A is harmonised with Australia and Canada.

An increase in the allowed limit to 20,000 IU (11.5 mg retinyl palmitate, or 6 mg retinol equivalents) will de-harmonise the Medicines Schedule with respect to these countries.

6. Interactions with other medicines.

No information was provided by the applicant. The National Institutes of Health Office of Dietary Supplements states that vitamin A has the potential to interact with several medicines, such as weight-loss drugs including orlistat and synthetic forms of Vitamin A (such as acitretin and bexarotene) used to treat skin conditions such as psoriasis or the skin effects of T-cell lymphoma (ODS, 2013).

7. Contraindications and precautions.

No information was provided by the applicant.

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.

Vitamin A toxicity can cause dizziness, nausea, headaches, coma, and even death. High intakes of preformed vitamin A in pregnant women can also cause birth defects in their babies (Azais-Braesco and Pascal, 2000; FDA 1995; FNB, 2002).

10. Potential for abuse or misuse.

Vitamin A is not habit-forming or a drug of abuse. No potential for abuse or misuse is anticipated.

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