Application for inclusion of Vitamin A (Retinol Palmitate) 50 000 IU and 100 000 IU capsules on the WHO Model of Essential Medicines

Submitted by

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Acknowledgement to Dr San Beggs for his kind assistance

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1. Summary statement of the proposal for inclusion or change

Vitamin A deficiency is a major public health problem throughout the world, especially in preschool children. Vitamin A deficiency contributes significantly to the morbidity and mortality of this age group. While WHO recommend vitamin A supplementation, there is not an appropriate oral dosage form listed on the current Formulary for children less than 12 months of age.
The current recommendation for supplementation is:
< 6 months 50 000 IU
6-12 months 100 000 IU
> 12 months 200 000 IU
It is proposed to include the appropriate formulations to support this recommendation of 50 000 IU and 100 000 IU dosages, in the form of retinol palmitate capsules. A 200 000 IU preparation is already available to support the recommendation for children over 12 months of age.

2. Name of the focal point in WHO supporting the application

Bruno de Benoist, Coordinator, MNM Unit

3. Name of the organization(s) consulted and/or supporting the application

Department of Clinical Pharmacology, Royal Children's Hospital, Melbourne, Australia

Centre for International Child Health, Department of Paediatrics, University of Melbourne, Australia

Child and Adolescent Health and Development department, WHO

4. International Non-proprietary Name of the medicine

Retinol

5. Formulations proposed for inclusion

a. Retinol (as palmitate) 50 000 IU per capsule
b. Retinol (as palmitate) 100 000 IU per capsule

6. International availability

a. This formulation is currently made by Pharmalab, Sydney Australia[1].
b. This formulation is currently available via UNICEF procurement services[2].

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

This is an individual medicine.
Other formulations for retinol are on the existing list of essential medicines.

8. Information supporting the public health relevance

Epidemiology of Vitamin A deficiency:
Vitamin A deficiency is a major public health problem in the developing world. Worldwide it is the second most common nutritional disease, after protein-calorie malnutrition[3]. Each year, 250 million children are at risk of vitamin A deficiency worldwide[4]. At greatest risk are pre-school aged children and women of reproductive age, with the peak incidence seen in children aged six months to two years.

Vitamin A is essential for multiple functions, including for development and maintenance of normal vision, is required for gene expression, normal immune function, growth and development and for the maintenance and proliferation of epithelial cells[5]. Clinical vitamin A deficiency results in xerophthalmia, the severity of which ranges from night blindness to corneal ulceration and permanent blindness. Subclinical deficiency may be reflected in reduced serum or breast milk retinol levels[6], and results in increased susceptibility to common infectious diseases. An estimated 1.3-2.5 million infant and preschool deaths annually can be attributed to vitamin A deficiency[7].

Infants initially rely on breast milk for supply of vitamin A, in addition to any stores accumulated in the third trimester of pregnancy. Maternal vitamin A status will determine how much vitamin A can be provided for the infant in the absence of supplementation[6]. Non-breastfed infants are at particularly high risk of developing vitamin A deficiency, although fortunately in many of the countries at greatest risk of vitamin A deficiency there are very high rates of breast feeding, including beyond six months of age[8].

In addition to the essential role of vitamin A to maintain normal vision, the role of vitamin A in reducing the morbidity and mortality of childhood illnesses, particularly measles, has been well established. Measles remains a major cause of morbidity and mortality in developing countries, where hospital fatality rates are often reported as >10%[5]. There are approximately 36.5 million cases of measles each year, resulting in over one million deaths[9]. There is also evidence that measles infection in well-nourished children can reduce serum retinol levels to less than those observed in malnourished children without measles[10].

Current supplementation programs:

a. Universal distribution/Primary prophylaxis:
Most prophylactic programs for vitamin A supplementation target preschool aged children and postpartum women, as these are the groups at greatest risk of vitamin

A deficiency and subsequent morbidity and mortality. Universal distribution programs aim to supply all people in areas of known vitamin A deficiency or at risk of deficiency, with high dose vitamin A every 4-6 months to maintain adequate body stores. Successful programs have typically been linked with other public health measures, such as immunisation programs. An approach of universal distribution aims to prevent the development of vitamin A deficiency.

b. Targeted prevention programs provide high doses of vitamin A to those considered 'at-risk' of vitamin A deficiency, such as children with measles and other severe childhood illnesses such as diarrhoea, respiratory disease and chickenpox.

c. Treatment of clinical vitamin A deficiency, xerophthalmia, is also essential to prevent permanent blindness. Development of night blindness should be considered an emergency and high dose vitamin A should be provided immediately. 95% of corneal lesions improve or heal within one week of treatment[11].

9. Current Treatment guidelines/details

a. Prevention of Vitamin A deficiency – Universal distribution:

0-6 months old:

The current WHO guidelines are varied. Previously only infants who were not being breast fed or whose breastfeeding mothers had not received supplementation postpartum, were recommended to receive a single dose of 50 000 IU at some point in the first six months of life. The ideal timing was not clearly specified[12]. This has subsequently been reviewed in 2000 and the most recent recommendation from WHO is to provide 50 000 IU at 6, 10 and 14 weeks of age, in conjunction with immunisations[13]. This is not reflected in the current Formulary however, which continues to recommend a single dose only[14].

In children over 6 months of age, there is general consensus and consistent guidelines for supplementation: The current guidelines recommend[12]:

Infants 6-12 months of age
100 000 IU every 4-6 months

Children >12 months of age
200 000 IU every 4-6 months

Post-partum women
2 doses x 200 000 IU within 6 weeks of delivery, minimum 24 hours between doses

Historically a single dose of vitamin A was given to women in the postpartum period. A recommendation to include a second dose was endorsed by WHO in 2000[13], which has been shown to maintain higher breast milk concentration for at

least six months, with a subsequent reduction in the incidence of respiratory infections and febrile illnesses in the infants[15].

b. Treatment of xerophthalmia in children

Immediately on diagnosis

< 6 months of age	50 000 IU
6-12 months of age	100 000 IU
> 12 months of age	200 000 IU

Next day

Repeat same age-appropriate dose

At least 2 weeks later

Repeat same age-appropriate dose

c. Targeted prevention of high-risk children

High risk = with measles, diarrhoea, respiratory disease, chickenpox, other severe infections or severe protein-energy malnutrition, or who live in vicinity of children with clinical vitamin A deficiency.

Infants < 6 months of age	50 000 IU
Infants 6-12 months of age	100 000 IU
Children > 12 months of age	200 000 IU

Additional dose should be given following day in hospitalised children with measles infection.

10. Summary of comparative effectiveness in a variety of clinical settings

Multiple Cochrane reviews have been undertaken to determine the efficacy of vitamin A supplementation, in both treatment and preventative strategies, in multiple clinical contexts. In addition to these meta-analyses, other large randomised controlled trials have addressed other issues surrounding vitamin A supplementation.

a. Measles infection:

Ellison first documented the protective effect of vitamin A supplementation on measles mortality in 1932[16]. Since that time both targeted and universal distribution regimes have been introduced in areas at risk. A meta-analysis in 1993 demonstrated a reduction in all cause mortality by 33% and a 66% reduction in mortality of hospitalised children with measles following a targeted prevention strategy of vitamin A supplementation[17].

A more recent Cochrane review was undertaken, including all randomised controlled trials in children <15 years old with measles. Eight studies met the

inclusion criteria, of which five were double blind, including a total of 2574 patients. These included both community based and hospitalised children. No significant overall reduction in mortality of children with measles was found when looking at the pooled data (RR 0.83; 95% CI 0.51-1.34), however subgroup analysis demonstrated a significant reduction in all cause mortality and pneumonia-specific mortality in *hospitalised* children aged less than two years of age, who received two high doses of vitamin A (RR 0.33; 95%CI 0.08-0.92). Only two studies commented on the effect of supplementation on the average length of hospital stay, which was reduced by 4.7 days in one study, and 0.5 days in another[5].

b. Non-measles pneumonia:

Acute respiratory tract infections, particularly pneumonia, are a leading cause of death in children less than five years of age in the developing world. There are estimated to be 150.7 million new cases of pneumonia each year in developing countries, resulting in 3.8 million childhood deaths annually, of which 30% are aged less than five.

A Cochrane review to determine the effect of vitamin A supplementation at the time of diagnosis, included parallel-arm, randomised and quasi-randomised controlled trials of children < 15 years old with non-measles pneumonia. Five trials were included, with a total of 1453 children. This review failed to demonstrate a significant reduction in mortality or length of hospital stay following high dose supplementation as targeted prevention – similar to the targeted prevention in children with measles[18]. There was the suggestion that those who received supplementation were *more* likely to require oxygen, reflecting increased severity of illness, compared to those who received placebo[19]. Subsequently targeted prevention of children with non-measles pneumonia is not recommended.

c. Primary prevention for infants < 6 months old:

At this point in time there has not been an extensive review of impact of vitamin A supplementation in infants less than six months of age. In this group, breastmilk is the major source of vitamin A and therefore liver stores at birth and maternal vitamin A status will determine the subsequent status of the infant.

In addition to the inclusion of three doses of 50 000 IU of vitamin A at the time of immunisation in these infants, there have been suggestions that a dose be administered as soon after birth as possible[13]. This follows two randomised placebo-controlled trials in Asia, which have shown a substantial reduction in infant mortality. The first of these included 2067 neonates born at a large hospital in Indonesia and reported a marked reduction in infant mortality (RR=0.36; 95% CI = 0.16-0.87)[20]. The other included 11 619 newborns in a community-based study in southern India. This demonstrated at 22% reduction in total mortality in infants aged less than six months who were supplemented with vitamin A at birth (95% CI = 4-37%)[21]. The vitamin A had an impact on mortality between two weeks and three months after supplementation.

d. Primary prevention for infants and children >6 months old:

While there has not been a Cochrane review to establish efficacy of this approach to vitamin A supplementation, there has been a large randomised control trial reported from Ghana[22, 23] and a substantial retrospective review of the impact of vitamin A supplementation, particularly in Vietnam and the Philippines[24].

The study in Ghana included almost 22 000 children, aged from 6-90 months, who were randomly assigned to receive high dose vitamin A – 200 000 IU if >1 year old, 100 000 IU if 6-12 months old – or placebo, at four monthly intervals. There was both a 'survival' arm, including 21 906 children who were followed for up to 26 months, equalling over 33 000 child years, and a 'health' arm including 1455 children who were assessed weekly for 12 months. A significant reduction in overall deaths (p=0.03), hospital admissions (p=0.02) and clinic attendances (p=0.001) was demonstrated in the supplemented group. In particular there was a significant reduction in anorexia and vomiting, and mortality secondary to acute gastroenteritis in this group, although the overall incidence of diarrhoea was unchanged. All other causes of mortality were reduced, except those secondary to non-measles pneumonia and malaria. Overall, the conclusion was that regular vitamin A supplementation reduced the frequency of severe and lethal illness, without demonstrating a clear effect on less severe illness[22, 23].

In the retrospective review data from WHO on supplement activities were combined with United Nations Population Division mortality date to estimate the number of deaths averted, costs associated and cost-effectiveness of such programs. This review focused particularly on campaigns conduced in 1998 and 1999, which had linked supplementation with immunisation programs targeting children aged 6-59 months in countries with known vitamin A deficiency. More than 94 million doses of vitamin A were administered in 1998, and more than 97 million in 1999. Coverage of over 80% was achieved in the majority of countries. If at least two doses of vitamin A were received during one calendar year, the estimated reduction in all-cause mortality was 23%, which is consistent with other meta-analyses[25]. If only one dose was received during the year, mortality was reduced by 11.5%. In Vietnam, a program of vitamin A supplementation demonstrated an greater than 85% effectiveness in preventing xerophthalmia, with similar estimates in the Philippines, depending on the level of coverage achieved[24].

e. Maternal supplementation to prevent mother-to-child transmission of HIV:
Approximately 2000 new paediatric cases of HIV are diagnosed each day worldwide, over 90% of which are in sub-Saharan Africa. The majority of paediatric infections are the result of mother-to-child transmission, either intrapartum, peripartum or via breastmilk. A Cochrane review identified four trials of intrapartum supplementation of vitamin A to assess effect on HIV transmission rates. A total of 3033 HIV-positive women and infant pairs were included. There was no significant reduction in vertical transmission of HIV from mother to child (OR 1.14; CI 0.93 to 1.38). There was however a significant increase in subsequent birth weight of the infants of supplemented mothers compared to controls (weighted mean difference 89.78, 95% CI 84.73 to 94.83)[26].

f. Supplementation in very low-birth-weight infants:
Vitamin A is essential for normal lung growth. Low birth weight infants, which are typically preterm are also at increased risk of developing chronic lung disease

and are likely to have low vitamin A stores at birth, as the majority of liver stores are achieved during the third trimester[27]. A recent Cochrane review included only randomised and quasi-randomised studies of the effect of vitamin A supplementation vs. placebo or no supplementation on very low birth weight infants (defined as </= 1500g or less than 32 weeks gestation). Outcomes included survival, chronic lung disease, bronchopulmonary dysplasia and vitamin D concentrations. Seven studies were included and reported outcomes on 631 infants treated with vitamin A and 620 controls. The method and dose of vitamin A varied between studies. Pooled data show a significant reduction in death or oxygen use at one month of age in infants who received vitamin A supplementation (RR 0.93; 95% CI 0.88-0.99)[27].

g. Supplementation during pregnancy:

Retinol is known to be teratogenic in high doses, particularly in early pregnancy. High maternal levels have been associated with spontaneous abortion and congenital malformations[28]. There is however a safe level of ingestion, aimed at preventing night-blindness in women and providing adequate vitamin A for growth and development of the foetus[29].

A Cochrane review was undertaken to determine the effectiveness of vitamin A supplementation during pregnancy, with or without other supplements, on maternal and newborn morbidity and mortality. At total of five trials which were either randomised or quasi-randomised were included, involving a total of 23 426 women[29]. Due to the heterogeneity of the trials, a meta-analysis was not possible. The largest study included over 20 000 women in a community based setting in southern Nepal. There was a reduction in all cause maternal mortality up to 12 weeks postpartum in the supplemented group (RR 0.60; 95% CI = 0.37-0.97)[30] but without any impact on foetal or early infant survival, nor on mortality of live born babies at six months of age[31].

h. Supplementation during breastfeeding:

A protocol for a Cochrane review to assess the impact on both mothers and infants of vitamin A supplementation for breastfeeding woman exists, however there is not currently data available regarding outcome of this review[6].

i. Comparison of oil vs. water based formulations:

High dose formulations of vitamin A are usually gelatin capsules, which can be swallowed by adults and older children. In infants and younger children the oil-based solution can be removed by syringe or squirted from theses capsules, or a dose can be measured from a 100ml bottle of an oil-based solution. A dispenser for this purpose has been developed, which provided 0.5ml with each stroke of the plunger, being equivalent to a dose of 50 000 IU each time. Water-based preparations also exist, however oil-based are preferred for oral administration. Only water-based preparations should be injected intramuscularly but this should rarely be required. Oil-based preparations are usually well-absorbed following oral administration[12].

The stability and therefore activity of vitamin A are affected by exposure to sunlight and temperature changes. An oil-based solution stored unopened in an opaque container is estimated to have a shelf life of at least 2 years. Once a container has been opened, potency gradually reduces and the recommendations

are that once opened, the contents should be used within 6-8 weeks. Preparing the oil-based solution in capsules provides some protection against this loss of potency. Currently, as only 200 000 IU capsules are listed on the essential medicines list, usual practise when a lower dose is required is to approximate the dose from these capsules[12]. This results in both inaccurate dosing and significant waste. Storage and transportation of capsules is also preferable to solutions in bottle.

11. Summary of comparative evidence on safety

Many millions of doses of Vitamin A have been given over the last 20 years, including in high dose regimes, without any severe side-effects being reported[13]. Multiple randomised control trials demonstrate that high dose Vitamin A supplementation may be associated with transient side effects but there is no evidence of any permanent or long-term sequelae[4, 8, 9, 13, 19, 20].

The most common side effects reported include a bulging fontanelle, vomiting and irritability. These symptoms are thought most likely to represent an increase in intracranial pressure, however one placebo-controlled trial of 1597 infants did not demonstrate an increased intracranial pressure on Doppler ultrasound in those with bulging fontanelles[20]. The increased incidence of bulging fontanelle has been reported at between 1-2% when compared with placebo, with resolution being demonstrated in the majority by 48 hours after ingestion[4, 8, 13, 20]. Vomiting following ingestion was most common in infants less than six months old but again was transient and self-limited[8, 13]. In addition, there is also clear evidence that administration of vitamin A supplements in high doses at the time of immunization does not alter their subsequent immune response and rate of seroconversion[4].

Acute vitamin A toxicity may follow doses of 20 times the RDA in children and chronic toxicity may result from prolonged (months to years) high dose intake[32]. A transient increase in serum retinol levels has been demonstrated after high doses in children, but this is not considered to accurately reflect body stores of vitamin A and does not have any serious or lasting effects[3]. All symptoms of toxicity are reversible on cessation of dosing. A Cochrane review on high dose vitamin A supplementation in children with measles did not identify any reports of acute toxicity or any significant adverse events[5].

There has been one report of fourteen deaths and multiple illnesses following a campaign of vitamin A supplementation in India, where a change in measuring device *may* have lead to overdosing. The actual cause of these deaths is unclear, however it is unlikely that the deaths were related to the vitamin A dosing. Even the maximum possible dose received would not be expected to result in acute toxicity and death[33].

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

In 1993 The World Bank declared vitamin A supplementation one of the most cost effective of all health interventions[34]. Routine supplementation in children is particularly cost effective when linked with immunisation programs. The incremental cost increase when supplementation is linked with immunisation campaigns has been estimated as US$0.10 per child each time supplemented. Based on polio campaign data, the estimated cost of providing vitamin A alone to children is $US0.43 per child per dose. This data has then been extrapolated to estimate the incremental and average cost per death. The incremental cost per death averted was US$64-72 and the average cost per death averted ranged from US$276-310. Actual costs will vary depending on the country, campaign strategy, coverage achieved and child mortality rate. Incremental costs per death averted declined exponentially as child mortality rates increased[24].
Another study analysed the prevented cases and deaths due to pneumonia, diarrhoea and measles in children aged less than 5 years old. These were converted to disability adjusted life years (DALYs), and comparison was made between two WHO defined regions with high child mortality in sub-Saharan Africa (Afr-E) and South East Asia (Sear-D)[35]. Highest gains were achieved when multiple interventions were bundled together.

The International Drug Price Indicator Guide include 100 000 IU formulations in both capsule and tablet form. Each capsule is estimated to cost US $0.02. This can be compared to 200 000 IU capsules, such as those currently in use, which have a median price of US $0.06, with a range from US $0.025 to $0.36. The current practise is to use 200 000 IU capsules and for those who only need 100 000 IU, remove approximately half for administration and discard the remaining. Depending on the formulation of 200 000 IU capsules distributed and therefore the associated cost, a clear cost-benefit may be seen by including 100 000 IU capsules and removes the issue of approximating the dose and discarding a valuable supplement.

Pricing for the 50 000 IU capsule or an appropriate solution, is not available on the International Drug Price Indicator Guide. This formulation is however currently listed in MIMS at a cost of approximately US $35.68 for 100 capsules on private prescription. Direct and bulk purchase from a supplier directly would likely be significantly cheaper.

13. Summary of regulatory status of the medicine

Retinol palmitate (Vitamin A) 50 000 IU capsules

Available in Australia:
Retinol, Pharmalab
MIMS Abbreviated Prescribing Information
Section: 21(d) Fat-soluble vitamins
Uses/Indications: Vit A deficiency; premenstrual tension, URTI prophylaxis
Pack: 50,000 U [100] Private: $46.94AU ($1AU=$0.76US)

Retinol palmitate (Vitamin A) 100 000 IU capsules

We were unable to source a regulated formulation at this point in time.

14. Availability of pharmacopoeial standards

Paediatric Pharmacopoeia, Royal Childrens Hospital, Melbourne, Australia. (13th Edition)
(http://www.rch.org.au/pharmacy/dev/?doc_id=2107)

MIMS Annual 2006, Australia (30th Edition). MIMS Australia

MICROMEDEX 2006. Thomson MICROMEDEX® Healthcare Series USP DI®
(http://www.micromedex.com/)

15. Proposed (new/adapted) text for the WHO Model Formulary

Retinol palmitate (Vitamin A) 50 000 IU capsules
Retinol palmitate (Vitamin A) 100 000 IU capsules

Other formulations of retinol include:

Retinol palmitate 200 000 IU capsules
Retinol palmitate 10 000 IU tablets
Retinol palmitate 100 000 IU/ml oily solution in multidose dispenser
Retinol palmitate 100 000 IU in 2ml water-miscible ampoule for injection

Uses:

1. Prevention of Vitamin A deficiency
2. Targeted prevention of high risk children
3. Treatment of Vitamin A deficiency (xerophthalmia)

Precautions:

Pregnancy, breastfeeding

Dosage:

1. Prevention of Vitamin A deficiency – Universal distribution

Infants < 6 months of age

50 000 IU with diphtheria/pertussis/tetanus immunizations at 6, 10 & 14 weeks of age

Infants 6-12 months of age

100 000 IU every 4-6 months

Children >12 months of age

200 000 IU every 4-6 months

Post-partum women

2 doses x 200 000 IU within 6 weeks of delivery, minimum 24 hours between doses

2. Treatment of xerophthalmia in children

Immediately on diagnosis

< 6 months of age	50 000 IU
6-12 months of age	100 000 IU
> 12 months of age	200 000 IU

Next day

Repeat same age-appropriate dose

At least 2 weeks later

Repeat same age-appropriate dose

3. Targeted prevention of high-risk children

High risk = hospitalised children less than 2 years of age with measles, OR any child who has not received prophylactic vitamin A recently in any area where significant incidence of malnutrition and/or vitamin A deficiency.

Infants < 6 months of age	50 000 IU
Infants 6-12 months of age	100 000 IU
Children > 12 months of age	200 000 IU

An additional dose should be given following day in hospitalised children with measles infection.

Adverse Effects:

No serious or irreversible adverse effects in recommended doses.
High levels in pregnancy may cause birth defects.
Transient increased intracranial pressure and/or tense and bulging fontanelle in infants with high doses.
Transient vomiting, irritability in infants.
Massive overdose can cause rough skin, dry hair, an enlarged liver, a raised erythrocyte sedimentation rate, raised serum calcium and raised serum alkaline phosphatase concentrations.

16. References

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