PRODUCT MONOGRAPH

[Pr] Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation

Vitamin A and Vitamin E Softgel Capsules

100,000 IU Vitamin A (all-trans-retinyl palmitate) and 20 IU Vitamin E (all-rac-alpha-tocopheryl acetate)

One IU of Vitamin A is equivalent to the activity of 0.3 mcg of all-trans-retinol

ATC code: Vitamins – A11

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Softgel capsule/ 100,000 IU Vitamin A (all-trans-retinyl palmitate) and 20 IU Vitamin E (all rac-alpha-tocopheryl acetate)	None. *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

BACKGROUND

Vitamin A is an essential nutrient; it cannot be synthesized by the human body and therefore must be obtained through diet. Vitamin A is required for normal functioning of the visual system, maintenance of cell function for growth, epithelial integrity, red blood cell production, immunity and reproduction (FAO, 2001; Drug Bank, 2013; EFSA, 2015). Vitamin A deficiency (VAD) is common in the developing world. According to a 2009 World Health Organization (WHO) report (WHO Global Prevalence of VAD, 2009), about 190 million children under the age of 5 are Vitamin A deficient (i.e. serum retinol < 0.70 µmol/L), representing about 33% of children under age 5 in populations at risk of VAD (Imdad *et al*., 2010; NIH ODS, 2016). VAD of sufficient duration or severity can lead to disorders that are common in VAD populations such as xerophthalmia, the leading cause of preventable childhood blindness and a cardinal indicator of VAD (Imdad *et al*., 2010; NIH ODS, 2016). Although night blindness and Bitot's spots are considered mild stages of eye disease, both represent moderate-to-severe systemic VAD. Africa and South-East Asia contain the highest proportions of children under age 5 with biochemical VAD (Imdad *et al*., 2010). Oral Vitamin A supplementation (VAS) and food fortification are the most direct methods for providing Vitamin A to people whose diets are deficient (Imdad *et al*., 2010). The suggested VAS scheme for infants 6 – 11 months of age is one administration of 100,000 IU of Vitamin A and 200,000 IU of Vitamin A to children 12-59 months of age (every 4 – 6 months) in areas where VAD is a public health problem (WHO Guideline, 2011).

INDICATIONS AND CLINICAL USE

Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation [Vitamin A (all-trans-retinyl palmitate) and Vitamin E (all rac-alpha-tocopheryl acetate)] is indicated for prevention of the sequelae of Vitamin A deficiency (VAD) such as night blindness, Bitot's spots, and xerophthalmia in children 6-11 months of age in geographic areas where VAD is prevalent

Pediatrics (6 months to 11 months of age):
Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation is indicated for children 6 -11 months of age.

CONTRAINDICATIONS

- Hypervitaminosis of Vitamin A (Bauernfeind, 1980)
- Vitamin A supplementation (VAS) should not be used in infants and children in settings where Vitamin A deficiency (VAD) is not a public health problem.
- High dose VAS is contraindicated in pregnant women or women who may become pregnant (Buss *et al.,* 1994)
- Infants younger than 6 months of age including preterm neonates (WHO Guideline, 2011)
- Known hypersensitivity to Vitamin A, vitamin E or any ingredient in the formulation. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

General

Protect from moisture, light, and high temperatures above 30°C (CPID 2.3.P.8.1 Stability Summary and Conclusions).

High dose VAS should be only given to children under medical supervision in areas with confirmed VAD.

There is a potential interaction between VAS and vaccination; children should never be given high dose VAS concomitantly with vaccines especially with measles vaccine and diphtheria-tetanus-pertussis (DTP) vaccine (see **Drug-Drug Interactions**).

Single vitamin A deficiency is rare. Multiple vitamin/microelement deficiencies are expected in any dietary deficiency.

Most of the body's vitamin A is stored in the liver, and normally mobilized and released into the plasma as retinol. Though plasma retinol levels are useful for assessing vitamin A deficiency (i.e., a serum retinol 0.70 µmol/L or lower, WHO Guideline, 2011), serum retinol levels do not reflect vitamin A liver storage (NIH ODS, 2016).

Endocrine and Metabolism
The long term effect of the exposure to high dose VAS in terms of effect on bone resulting in increased bone resorption and decreased bone formation has not been studied. Caution should be exercised to avoid unintentional exposure to multiple large doses over a short period of time (SCF, 2002).

Opthalmologic
Supplementation with high dose of VAS may not prevent all cases of xerophthalmia (Tapan B, Donaldson D. Intestinal absorption in health and disease: micronutrients. Best Practice and Research Clinical Gastroenterology. 2003; 17(6): 957-979.
West and Sommer, 1987).

Respiratory
VAS should be given with caution to children with respiratory infections (EFSA, 2015, McLaren and Kraemer, 2012).

Special Populations

Pregnant Women: High dose VAS is contraindicated in pregnant women or women who may become pregnant due to the known teratogenic potential of Vitamin A (Buss *et al.,* 1994; EFSA, 2015) (see **CONTRAINDICATIONS and TOXICOLOGY**).

Among the babies born to women who took more than 10,000 IU of preformed Vitamin A per day in the form of supplements, it is estimated that about one infant in fifty-seven had a malformation attributable to Vitamin A. The malformations involved craniofacial, central nervous system, cardiac, and thymic structures (Rothman *et al*., 1995).

Nursing Women: Vitamin A is excreted in breast milk; contact your healthcare professional if you are breastfeeding (EFSA, 2015).

Pediatrics (6 - 11 months of age):
This product is only intended for children 6 - 11 months of age (WHO Guideline, 2011).

Refer to the Product Monograph for Vitamin A (200,000 IU) and Vitamin E (40 IU) Oral Liquid Preparation as Softgel Capsules for children 12 -59 months of age.

VAS is contraindicated in infants younger than 6 months of age (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The clinical presentation of vitamin A toxicity in infants and young children varies widely. The more commonly recognized signs and symptoms include skeletal abnormalities, bone tenderness and pain, increased intracranial pressure, desquamation, brittle nails, mouth fissures, alopecia,

fever, headache, lethargy, irritability, weight loss, vomiting, and hepatomegaly (Bush and Dahmas, 1984; IOM, 2001).
In most children 6–59 months of age, a dose of 100,000–200,000 IU of vitamin A is well tolerated, although side-effects such as headache, nausea or vomiting, and diarrhoea have been reported in 3–7% of these children. However, these symptoms are transient, with the large majority starting and disappearing within 24 hours of dosing (Bauernfeind, 1980; WHO Guideline, 2011).

Adverse effects within 48 hours of receiving VAS are usually mild and transient, with no long-term consequences. Adverse effects may include bulging of open fontanelles in younger infants, and nausea and/or vomiting and headache in older children with closed fontanelles (WHO Guideline, 2011).

There are no known deaths attributed solely to vitamin A toxicity due to overconsumption of Vitamin A (Bauernfeind, 1980; WHO Guideline, 2011).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Single periodic high dose side effects:
A systematic review assessing the safety and efficacy of supplementation with 100,000 – 200,000 IU Vitamin A, has been reported (Imdad *et al*., 2010; WHO Guideline, 2011). Three trials (Sinha, 1976; Florentino, 1990; Arya, 2000) reported a significantly increased risk of vomiting within the first forty-eight hours of supplementation. In these trials, there was a significantly increased risk of vomiting from 2% to 6%, in participants exposed to high dose VAS compared with those non-exposed to high dose VAS (relative risk (RR) of 2.75, 95% Confidence Interval (CI) 1.81-4.19).

Three trials (Stabell, 1995; Bahl, 1999; Arya, 2000; Imdad *et al*., 2010) reported bulging fontanelles, but data from only one trial could be analyzed. The significantly increased risk of bulging fontanelle was reported in neonates (one infant) exposed to high dose VAS compared to non-exposed (RR of 5.00, 95% CI 0.24-103.72). Most studies included children over 1 year of age and would not have assessed this side effect.

DRUG INTERACTIONS

Overview
While no drug-food, drug-herb, drug-laboratory, and drug-lifestyle interactions are currently known, drug-nutrient interactions, and drug-drug interactions may exist. Drug interactions are presented for the intended population in children.

Drug-Drug Interactions
Diphtheria-tetanus-pertussis (DTP) vaccine - There is potential interaction between high dose VAS and vaccination; children should never be administered high dose VAS concomitantly with vaccines especially with the measles and DTP vaccines (see **WARNINGS AND PRECAUTIONS**).

Measles vaccination: When VAS is administered in conjunction with the measles vaccination, there are documented cases in the literature of adverse side effects within 24 hours of dosing including: vomiting, loose stools, fever, and irritability (Imdad *et al*., 2010) (see **WARNINGS AND PRECAUTIONS**).

Drug-Nutrient Interactions
Calcium: Administration of large doses of Vitamin A for long periods of time can promote bone loss (EFSA, 2015; IOM, 2001).

Vitamin D: Vitamin A may antagonize the action of vitamin D (EFSA, 2015).

Vitamin E: Large doses of vitamin E can interfere with the absorption of Vitamin A (IOM, 2001).

Zinc: Zinc deficiency may interfere with Vitamin A metabolism through several mechanisms, including its absorption, transport and utilization (IOM, 2001).

The potential for Vitamin A interaction with other nutrients cannot be excluded; the effect of such interaction has not been fully characterized.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Children 6-11 months of age:

The recommended dose is one (1) administration (single dose) of Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation to children 6-11 months of age by a healthcare professional in areas where VAD is a public health problem in accordance with WHO Guideline (WHO Guideline, 2011).

(For children 12-59 months of age, see the Product Monograph for 200,000 IU Vitamin A and 40 IU Vitamin E which is given every 4 to 6 months to children where VAD is a public health problem).

Determination of VAD as a public health problem involves estimating the prevalence of deficiency in a population by using biochemical and clinical indicators of Vitamin A status. The typical settings for VAS is in populations where the prevalence of night blindness is 1% or higher in children 24-59 months of age or where prevalence of Vitamin A deficiency (serum retinol 0.70 µmol/l or lower) is 20% or higher in infants and children 6-59 months of age (Imdad *et al*., 2010; NIH ODS, 2016).

Missed Dose
Only one dose should be administered to children 6-11 months of age.

Administration
Vitamin A (100,000 IU) and Vitamin E (20 IU) is supplied as a soft-gel capsule and administered as an oral liquid preparation from the capsule as follows:

- Cut capsule end.
- Squeeze drops into child's mouth until the capsule is empty.
- The capsule must not go in a child's mouth or be swallowed.

OVERDOSAGE

The administration of excessive amounts or overdoses of Vitamin A supplements can lead to toxicity, known as hypervitaminosis A and may occur if more than one dose is administered erroneously (WHO Guideline, 2011). The amount required to cause toxicity will vary among individuals and their age and hepatic function (Bauernfeind, 1980; WHO Guideline, 2011).

Symptoms of Overdose
Signs and symptoms of acute Vitamin A toxicity from a single dose or more, may be delayed for 8 to 24 hours and can include the following: nausea, vomiting, diarrhea, changes in humour (irritability, drowsiness, lethargy), increased intracranial pressure (headache, bulging of fontanels, diplopia, papilloedema), skin changes (erythema, pruritis, desquamation). Peeling of skin around the mouth may be observed from one to several days after ingestion and may spread to the rest of the body. Increased plasma concentrations of Vitamin A may occur, but do not necessarily correlate with toxicity (Miller and Hayes, 1982; Bendich and Langseth, 1989; Hathcock *et al*., 1990; CPS, 2016; Parfitt, 1999; WHO, Adverse Events, 2016).

The teratogenic effect of excessive intake of vitamin A or specific retinoids is well documented, in both animals and humans (Hathcock *et al.*, 1990) (see **TOXICOLOGY**).

Management of Overdose
If Vitamin A toxicity occurs, provide symptomatic and supportive treatment. For an acute overdose, activated charcoal should be used to achieve gastrointestinal decontamination. Intracranial pressure may be reduced with intravenous (i.v.) dexamethasone or i.v. mannitol. In untreated children, increased intracranial pressure may persist for 4 weeks after discontinuation of Vitamin A (Combs, Gerald F. The Vitamins. Amsterdam: Elsevier/Academic Press, 2012. Print.
CPS, 2016).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Retinyl palmitate is a naturally-occurring phenyl analogue of retinol (Vitamin A). The term vitamin A comprises all-*trans*-retinol (also called retinol) and the family of naturally occurring molecules associated with the biological activity of retinol (fat soluble retinoids such as retinal, retinoic acid and retinyl esters), as well as the group of provitamin A carotenoids (such as β-carotene, α-carotene and β-cryptoxanthin) that are dietary precursors of retinol (EFSA, 2015).

Two forms of Vitamin A are available in the human diet:

- preformed Vitamin A (retinol and retinyl ester) found in foods from animal sources, including dairy products, fish, and meat (especially liver) (Higdon, 2000; NIH ODS, 2016), Free retinol is not generally found in foods, retinyl palmitate, a precursor and storage form of retinol is found in animal derived foods (Nutri-Facts, 2015), and
- provitamin A carotenoids are found in fruits and vegetables, with beta-carotene being the most important provitamin A carotene, others include alpha-carotene and beta-cryptoxanthin . These plant pigments are converted to Vitamin A by the body (Higdon, 2000; NIH ODS, 2016).

Preformed Vitamin A and provitamin A must be metabolized intracellularly to retinal and retinoic acid, the active forms of Vitamin A, to support the vitamin's important biological functions. Retinyl esters and provitamin A carotenoids are converted to retinol, which is oxidized to retinal and then to retinoic acid, most of the body's Vitamin A is stored in the liver in the form of retinyl esters (NIH ODS, 2016).

Mechanism of Action

Vitamin A is required for human growth and bone development, vision, reproduction, and the integrity of mucosal and epithelial surfaces (IOM, 2001; Ross, 2010; NIH ODS, 2016). Vitamin A compounds are fat-soluble molecules predominantly stored in the liver as retinyl esters (e.g., retinyl palmitate) (Higdon, 2000).

Retinyl esters are hydrolyzed to all-trans-retinol, which binds to retinol binding protein (RBP) and is released into the bloodstream. The all-trans-retinol/RBP complex binds to the transthyretin transport protein, which delivers all-trans-retinol to peripheral tissues (Higdon, 2000).

In the visual system, the retina contains two main types of light-sensitive photoreceptor cells: rod cells and cone cells. Retinol is transported to the retina via circulation and accumulates in retinal pigment epithelial (RPE) cells. There, retinol undergoes esterification to form retinyl ester, which can be stored (Higdon, 2000). When needed, retinyl esters are hydrolyzed and isomerized to form 11-cis-retinol, which can be oxidized to form 11-cis-retinal. 11-cis-retinal can travel to the rod cells, where it binds to the opsin protein and forms the visual pigment, rhodopsin (Higdon, 2000; EFSA, 2015). The absorption of light catalyzes the photoisomerization of 11-cis-retinal to all-trans-retinal in thousands of rods and its release, which triggers the signaling to the neuronal cells associated with the brain's visual cortex where it can be interpreted as vision. For vision to continue, 11-cis-retinal must be regenerated (IOM, 2001; EFSA, 2015). Regeneration of 11-cis-retinal requires the reduction of all-trans-retinol to retinol, transport of retinol from the rod cells to the RPE cells, and esterification of all-trans-retinol, providing the local storage of

retinyl esters (IOM, 2001). When needed, retinyl esters are hydrolyzed and isomerized to form 11-cis-retinol, which is oxidized to 11-cis-retinal and transported back to the photoreceptor cells for recombination with opsin to begin another photo cycle (Higdon, 2000; IOM, 2001).

Alteration of rhodopsin through a cascade of photochemical reactions results in ability to see objects in dim light. The speed at which rhodopsin is regenerated relates to the availability of retinol. Night blindness is usually an indicator of inadequate available retinol or failure to re-synthesize 11-cis-retinal rapidly (Drug Bank, 2013), but it can also be due to a deficit of other nutrients, which are critical to the regeneration of rhodopsin, such as protein and zinc, and to some inherited diseases, such as retinitis pigmentosa.

It is reported that vitamin E may increase absorption of Vitamin A; however, the exact role of vitamin E in the formulation has not been characterized.

Pharmacodynamics

In the small intestine, intestinal cells absorb retinol through a carrier mediated process involving the CRBPII protein. Once absorbed, retinol undergoes a re-esterification process and is contained in a chylomicron, which is then able to be secreted into the lymphatic duct. The fat soluble retinal ester is then stored in liver hepatocytes, through a receptor mediated process involving chylomicrons, for future use.

Vitamin A is a cofactor in various biochemical reactions including mucopolysaccharide synthesis, cholesterol synthesis, and hydroxysteroid metabolism. Vitamin A plays vital roles in vision, epithelial differentiation, growth, reproduction, pattern formation during embryogenesis, bone development, hematopoeisis, and brain development. It is also important for the maintenance of the proper functioning of the immune system (Drug Bank, 2013).

Pharmacokinetics

Absorption:

Vitamin A is a fat-soluble vitamin and readily absorbed from the normal gastrointestinal tract. Intestinal absorption of preformed Vitamin A occurs after retinyl esters have been processed in the lumen of the small intestine (IOM, 2001). Plasma concentrations reach a peak level within 3 to 5 hours (Combs, Gerald F. The Vitamins. Amsterdam: Elsevier/Academic Press, 2012. Print. CP, 2016). Seventy to ninety percent of Vitamin A from the diet is absorbed in the intestine (IOM, 2001; EFSA, 2015). The efficiency of absorption for Vitamin A continues to be high (60-80%) as intake continues to increase. Greater than 90% of the retinol store within the body enters as retinyl esters that are subsequently found within the lipid portion of the chylomicron. Absorption of Vitamin A is very rapid, with maximum absorption occurring two to six hours after digestion. A small percentage of dietary retinoid is converted to retinoic acid in the intestinal cell (IOM, 2001). The intestine actively synthesizes retinoyl β-glucuronide that is hydrolyzed to retinoic acid by β-glucuronide (IOM, 2001). For optimal retinoid absorption, fat must be consumed along with the newly ingested retinoid. This fat is needed to facilitate retinoid entry into enterocytes from the lumen of the gut as dietary retinyl esters are unable to enter intestinal mucosa and must be first hydrolyzed by retinyl ester hydrolase to yield free retinol (D'Ambrosio *et al*., 2011; EFSA, 2015). In addition, a fat load is required to allow for optimal

chylomicron formation, since retinoids, like other dietary lipids, enter the body as a component of nascent triglyceride-rich chylomicrons (D'Ambrosio *et al*., 2011). Within the intestinal lumen, the vitamin is incorporated into a micelle and absorbed across the brush border into the enterocytes. Within the enterocyte, precursors of Vitamin A (carotenoids) are converted to active forms of the vitamin. The newly formed products and additional precursors are then packaged into nascent chylomicrons and prepared for transport throughout the body by secretion into the lymphatic system for delivery to blood (EFSA, 2015).

Absorption can be incomplete in patients with fat malabsorption, low protein intake, hepatic or pancreatic disease. Any conditions that impair the luminal emulsification of fat, its hydrolysis, or micelle formation are likely to simultaneously reduce the absorption of Vitamin A (Ross, 2010). Additionally, recent fever and malaria may negatively affect absorption and retention of Vitamin A. Absorption of Vitamin A can be impaired in the presence of common gastrointestinal infections from giardia, ascaris, salmonella, and other entero−pathogenic organisms. Furthermore, common respiratory infections may also be expected to reduce absorption of a large dose of Vitamin A (i.e., during which absorption of physiologic doses of Vitamin A decreases from nearly 100% to about 75%) (McLaren and Kraemer, 2012).

Distribution:
With a series of metabolic steps, the absorbed retinol is reconverted to retinyl esters and is incorporated into chylomicrons within the intestinal cells. Chylomicrons are then released into the lymphatic channels to be delivered through the thoracic duct to general circulation. Once circulating, the majority of retinyl esters are removed from chylomicrons, hydrolyzed and taken up by liver cells. Some retinyl esters can be taken up directly by peripheral tissues, while Apoprotein E is required for the uptake of chylomicrons remnants by the liver. There they can be re-esterified and stored in adipocytes as retinol. Retinyl ester hydrolase catalyzes the hydrolysis of retinyl ester to retinol, following endocytosis (IOM, 2001). When needed (e.g., when retinol levels are low), retinol stores in the liver combine with retinol-binding protein (RBP) to form a RBP-retinol complex (holo-RBP). Holo-RBP is secreted into the blood and combines with the transthyretin transport protein to form a trimolecular complex with retinol (IOM, 2001).This larger complex circulates and delivers the required retinol to tissues by associating with specific membranes and binding proteins on those tissues that remove the retinol for use. The transthyretin-RBP-retinol complex circulates in the blood, delivering the lipophilic retinol to tissues; its large size prevents its loss through kidney filtration. Dietary restriction in energy, proteins, and some micronutrients can limit hepatic synthesis of proteins specific to mobilization and transport of Vitamin A. Vitamin A is also stored in the kidneys, lungs, adrenals, retinas and intraperitoneal fat in lesser amounts as retinyl palmitate (Tapan and Donaldson, 2003). Altered kidney functions or fever associated with infections (e.g., respiratory infections or diarrhea) can increase urinary Vitamin A loss. Normal adult body stores of Vitamin A are sufficient to meet the body's requirements for several months to 2 years. Vitamin A does not readily cross the placenta and is excreted in milk (Combs, 2012).

Metabolism:
Retinoid metabolism within the gastrointestinal tract occurs predominantly within the proximal portion of the small intestine and involves metabolic events that occur both in the lumen, as well as within the enterocyte (D'Ambrosio *et al*., 2011). The key digestive processes that occur within

the lumen of the intestine include the physical release of dietary retinoids from the food matrix and their emulsification with dietary fatty acids and bile acids (D'Ambrosio *et al*., 2011; EFSA, 2015). The mechanism through which retinol is taken up from the circulation by peripheral cells has not been conclusively established (IOM, 2001). Emulsification with free fatty acids and bile salts is necessary for micelle formation which is essential to facilitate uptake of the highly insoluble retinoids into enterocytes from the lumen (D'Ambrosio *et al*., 2011; Ross, 2010). Dietary retinol is taken up directly from the lumen into the enterocyte; however, dietary retinyl esters must first undergo enzymatic hydrolysis within the lumen or at the enterocyte brush border to allow for uptake of the hydrolysis product retinol (D'Ambrosio *et al*., 2011). Retinol is trapped intracellularly by re-esterification or binding to specific intracellular binding proteins. Retinyl esters together with other lipids are incorporated into chylomicrons, which are secreted into lymphatic system (D'Ambrosio *et al*., 2011). Chylomicrons are metabolized by lipoprotein lipase which releases their triglycerides as fatty acids into adipose and muscle tissues, and then the chylomicron remnant delivers the rest of their lipids and majority of retinyl esters to the liver (Ross, 2010). Retinol that is not immediately released into circulation by the liver, is re-esterified and stored in the lipid-containing stellate (Ito) cells of the liver until needed to maintain normal blood retinol concentrations (IOM, 2001).

Excretion:
Holo-RBP is filtered into the glomerulus but recovered from the kidney tubule and recycled. Only a relatively small fraction of retinol and its metabolites is excreted in urine; the majority of Vitamin A is excreted as inactive metabolites which result from tissue utilization and as potentially recyclable active glucuronide conjugates of retinol in bile secretions (IOM, 2001; Ross, 2010). When liver Vitamin A exceeds a critical concentration, the portion of excreted Vitamin A metabolites in bile increases; this is suggested as a protective mechanism for reducing risk of excess storage of Vitamin A (IOM, 2001). No single urinary metabolite has been identified which accurately reflects tissue levels of Vitamin A or its rate of utilization.

The majority of biliary products are released as feces, however, through enterohepatic circulation, 30% of the biliary products (i.e., retinoyl β-glucuronides) are reabsorbed back into the liver from the intestines. In terms of intake of Vitamin A in the diet, about 10% is not absorbed, 20% appears in the feces through the bile, 17% is excreted in the urine, 3% is released as CO_2, and 50% stored in the liver (Olson, 1994; McLaren and Kraemer, 2012).

STORAGE AND STABILITY

Keep container tightly closed, protected from moisture and light, in a cool, dry place. Avoid temperatures above 30°C and relative humidity above 65%.
Keep in a safe place out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms
Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation are supplied as blue tube shaped softgel capsules with a nipple tip to allow for cutting and administration, as a single-dose dispenser or a graduated spoon. Each softgel capsule contains: 100,000 IU Vitamin A (all–trans-

retinyl palmitate) and 20 IU Vitamin E (all-rac-alpha-tocopheryl acetate. One IU of Vitamin A is equivalent to the activity of 0.3mcg of all-trans-retinol. Each capsule contains a clear, colourless to pale yellow oil fill.

Composition
Medicinal ingredients: Vitamin A (all–trans-retinyl palmitate) and Vitamin E (all-rac-alpha-tocopheryl acetate).

Non-medicinal ingredients: D&C red #28, ethyl vanillin, FD&C blue #1, gelatin, glycerin, soy bean oil, titanium dioxide. May contain trace levels of lecithin.

Packaging
Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation softgel capsules are packaged in 300cc white high density polyethylene (HDPE) round 45/400 bottles. Each bottle contains 500 softgel capsules and a desiccant that consists of activated carbon and silica gel in printed Tyvek®.

Storage conditions: Keep container tightly closed, protected from moisture and light, in a cool, dry place. Avoid temperatures above 30°C and relative humidity above 65%.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Vitamin A:

Proper names: Vitamin A (Retinol Palmitate), Vitamin A Palmitate, Retinyl palmitate, retinol palmitate, all-trans-Retinyl palmitate, all-trans-Retinol palmitate

CAS number: 79-81-2

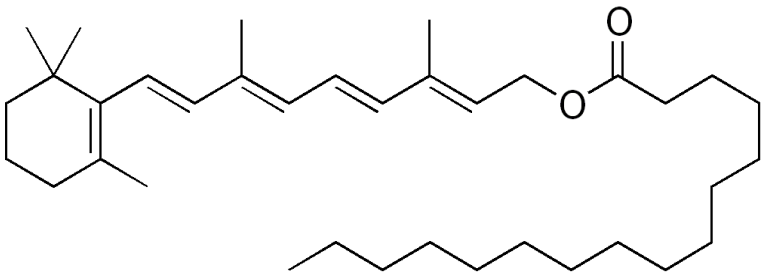
CAS Index Name: Retinol hexadecanoate

Chemical name: [(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraen-1-yl] hexadecanoate

Molecular formula: $C_{36}H_{60}O_2$

Molecular mass: 524.86 g/mol

Structural formula:

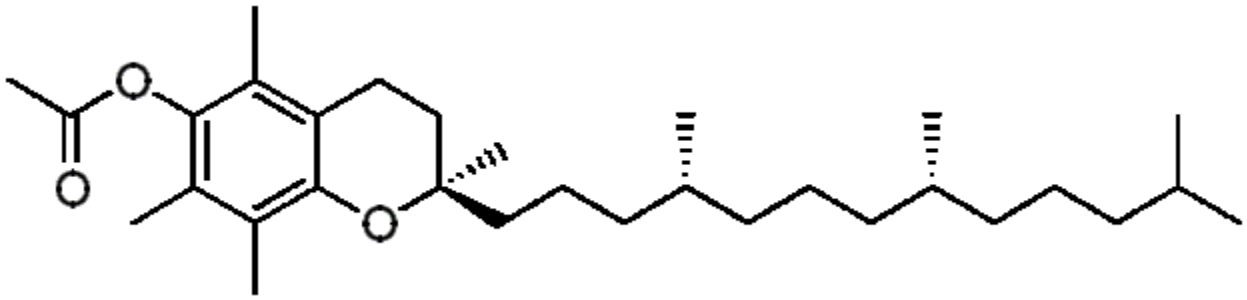


Physiochemical properties: Clear to hazy yellow to orange viscous liquid or semisolid with melting point of approximately 28°-29°C, and density of approximately 0.90-0.95 g/mL. Insoluble in water but soluble in chloroform, ether, and vegetable oils, i.e., corn oil, and slightly soluble in alcohol. Solid and solutions are sensitive to air, light and heat. Solutions are reasonably stable in the dark, at -20°C in peroxide-free and acid-free organic solvents (esters of retinol are more stable than retinol). Store solutions under an inert atmosphere, in the dark and at -20°C (Sigma-Aldrich, 2016a).

Vitamin E:

Proper name:	Vitamin E (dl-alpha-tocopheryl acetate), DL-a-Tocopherol acetate, Vitamin E acetate, Tocopherol acetate, Alpha-Tocopherol acetate; Tocopheryl acetate
CAS number:	7695-91-2 (tocopheryl acetate)
Chemical name:	[(2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-yl] acetate
Molecular formula:	$C_{31}H_{52}O_3$
Molecular mass:	472.743 g/mol

Structural formula:



Physiochemical properties:	Yellow, viscous liquid with boiling point > 200°C and density of 0.96 g/mol. Tocopherols are methyl-substituted hydroxychromans with a phytyl side chain. In general, have three asymmetric carbons, so there are eight possible diastereomers. Insoluble in water, and unstable to alkaline conditions. Miscible with ether, acetone, chloroform, and vegetable oils. Solutions remain active at 2–8 °C for several months. Solutions should be protected from light. (Sigma-Aldrich, 2016b).

CLINICAL TRIALS

Within 20 years of its discovery 100 years ago, vitamin A was recognized as critical to normal eyes, growth, and survival. Clinical interest demonstrated Vitamin A importance in preventing xerophthalmia (Sommer, 2014).

Information from various clinical trials has been reviewed extensively by expert groups over the years. The International Vitamin A Consultative Group (IVACG), UNICEF and WHO first came up with policy guidelines for the diagnosis, treatment and prevention of Vitamin A Deficiency Disorders in 1988 in a document entitled, "*Vitamin A Supplements: A Guide to Their Use in the Treatment and Prevention of Vitamin A Deficiency and Xeropththalmia*" (Reddy, 2002). A second edition of this guideline was issued in 1997. This strategy of periodic large doses of Vitamin A where there is a public health problem was officially endorsed in 1972 by UNICEF and WHO at a consultation convened in Hyderabad, India which was followed up by the WHO/UNICEF Joint Policy Committee and a recommendation from the WHO (WHO Guideline, 2011).

Further information on clinical trials from available published literature is provided in this section.

Published Literature

The use of high dose VAS to treat clinical eye signs or prevent blindness has been documented since the 1960s, when the widespread nature of xerophthalmia was a serious public health problem. The WHO sponsored the first pilot trial with high doses of Vitamin A (300,000 IU) in Jordan in 1965-66 (WHO Technical Report, 1976). In this pilot trial, infants aged three to six months received this high dose without adverse effects. Similar trials were conducted in India and Indonesia using oral dosing with 200,000 IU of retinyl palmitate in oil once every six months, the optimum regime for reducing the incidence of ocular lesions in a community without causing serious acute hypervitaminosis A symptoms (WHO Chronicle, 1973).

Following the first pilot trial in Jordan (1964-65), countries such as India (1970), Bangladesh (1973) and Indonesia (1973) began to implement pilot programs for the prevention of blindness in children using a 200,000 IU dose of Vitamin A with 40 IU vitamin E in an oil solution for oral administration given periodically (every four to six months). This became the most widely used dosage form for use in prevention of blindness and gained wide acceptance.

A comprehensive review was conducted on all available evidence for Vitamin A supplementation (100,000 IU to 200,000 IU) in children aged 6 months to 5 years which included 43 trials in about 215,633 children, Though mortality was the primary endpoint in many clinical trials, the systematic review/meta-analysis of VAS reported four trials with a 53% reduction in Bitot's spots prevalence (RR=0.45 (95% CI 0.33-0.61), while one trial reported no effect on Bitot's spots incidence (RR=0.93, 95% CI 0.76-1.14). One trial reported a 47% reduction in night blindness incidence (RR=0.53, 95% CI 0.28-0.99). Two trials reported a 68% reduction in night blindness prevalence (RR=0.32, 95% CI 0.21-0.50). Three trials reported no combined effect on xerophthalmia incidence while two trials reported a 69% reduction in xerophthalmia prevalence (RR=0.31, 95% CI 0.22-0.45) (Imdad *et al*., 2010).

In a cluster-randomized trial involving 1 million pre-school children in north India (DEVTA trial) VAS (retinol) was given every six months for five years. Groups were randomized to usual care, Vitamin A (retinol capsule of 200,000 IU retinyl acetate in oil) every six months, 400 mg albendazole (deworming tablet) every six months, or both (no placebo were used). Results of the DEVTA, demonstrated that estimated compliance with 6-monthly retinol supplements was 86% and amongst the 2581 children, allocation to VAS halved the prevalence of severe VAD (i.e., retinol <0.35 µmol/L) 1-5 months after treatment from 6% to 13%. The prevalence of Bitot's spots was also halved in the treatment group vs no VAS treatment from 1.4% to 3.5% (Awasthi, 2013). The majority of the studies evaluated the effect of high dose VAS for the proposed indication; the efficacy of lower dose for the same indication has not been sufficiently studied.

DETAILED PHARMACOLOGY

Animal Pharmacology

Vitamin A is essential for proper growth and is involved in many metabolic processes. Two main metabolites of Vitamin A are retinoic acid (an important intracellular messenger for cell differentiation) and retinal (an essential of visual pigment).Vitamin A is also actively involved in helping to maintain immune function. A study found that supplementing rats with a high dose of retinyl palmitate resulted in elevated phagocytic and tumoricidal activity of peritoneal macrophages; an important cell involved in immune defense (Edem, 2009; Moriguchi *et al*., 1985).

Animal Pharmacokinetics

Recent rat studies have determined that retinol palmitate absorption primarily begins in the intestinal tract. Vitamin A is converted into retinal esters and taken up by the lymphatic system. From there, Vitamin A is stored in the liver where it can be obtained for future use. Based on a rat study which used a radioactively labelled chylomicrons encompassing Vitamin A, the distribution of retinal palmitate after eight hours could also be traced in the kidney, lungs, adrenals, and plasma, with two-thirds of the radioactive Vitamin A detected in the liver (Goodman *et al*., 1965; D'Ambrosio *et al*., 2011). After twenty-four hours following administration, the majority of the radioactive Vitamin A (water soluble metabolites) was expelled from the body via biliary elimination and urine (Goodman *et al*., 1965). It has also been determined in piglets that regardless of dose amount, piglets with a high birth weight (>1.5 kg) were found to store more supplemental Vitamin A (VA) than low birth weight piglets (<1 kg) when administered at birth (Heying *et al*., 2015).

Recently, methods of mathematical modeling have begun to shed light on retinol kinetics in the postnatal growth period and on the effect of retinoid supplementation on retinol kinetics. Comparison of kinetic parameters from tracer studies in neonatal rats with those previously determined in models of VA metabolism in the adult suggests both similarities and differences in the relative transfer rates of plasma retinol to extrahepatic tissues, resulting in similarities and differences in kinetic parameters and inferences about physiologic processes. Similarities between neonatal and adult models include the capacity for efficient digestion and absorption of VA; characteristics of a high-response system; extensive retinol recycling among liver, plasma, and extrahepatic tissues; and comparable VA disposal rates. Differences between neonatal and

adult models include that, in neonates, retinol turnover is faster and retinol recycling is much more extensive; there is a greater role for extrahepatic tissues in the uptake of chylomicron VA; and the intestine plays an important role in chylomicron VA uptake, especially in neonatal rats treated with a supplement containing VA. In summary, retinol kinetic modeling in the neonatal rat has provided a first view of whole-body VA metabolism in this age group and suggests that VA kinetics in neonatal rats differs in many ways from that in adults, perhaps reflecting an adaption to the lower VA concentration found in neonates compared with adults (Tan *et al*., 2015).

Human Pharmacokinetics

To investigate whether Vitamin A supplementation results in elevated levels of retinoic acid compounds in human plasma, six healthy human males (aged 25-32) were provided with 833 IU of Vitamin A per kg in body weight, once a day for 20 days. Results found a significant rise (two fold) in trans-retinoic acid, (7 fold) in 13-cis-retinoic acid, and (5 fold) in 13-cis-4-oxoretinoic acid in comparison to retinoid endogenous plasma concentrations. Similar results have been found after treatment with isotretinoin, a known teratogenic drug (Eckhoff and Nau, 1990a).

The plasma concentration of certain retinoids associated with the intake of vitamin A through dietary sources and vitamin supplements was evaluated in a single and multi-dose study. In the single dose study, 36 adult females (≥18 years) were provided with a meal containing Vitamin A at levels of approximately 4,000, 40,000, or 80,000 IU. Plasma in both the single dose and multi-dose studies was analyzed using a high performance liquid chromatographic method with ultraviolet detection. Concentrations of 4-oxo-tretinoin were below the assay quantification limit (0.3 ng/mL) in the majority of samples collected. Based on data collected from the single dose study, a linear relationship between dose and Cmax and also dose and AUC for of isotretinoin and 4-oxo-isotretinoin were found. For isotretinoin the Cmax function was found to be 0.00016 x dose + 0.7 (r^2=0.56, P<0.001) and AUC to be 0.00498 x dose + 6 (r^2=0.69, P<0.001). For 4-oxo-isotretinoin Cmax function was found to be 0.00019 x dose + 0.3 (r^2=0.54, P<0.001) and AUC to be 0.0115 x dose -18 (r^2=0.55, P<0.001).

In the multi-dose study, 24 additional adult females were administered Vitamin A supplements at daily dose of approximately 5,000, 10,000, or 25,000 IU for 60 days. In this study, the levels of isotretinoin and 4-oxo-isotretinoin reached a steady state by day 15. Furthermore, the group receiving 5000 IU of Vitamin A showed a higher bioavailability in comparison to the 10,000 and 25,000 IU groups. Daily ingestion of 5000 IU of Vitamin A resulted in the 24 hour AUC of isotretinoin increasing by 141 + 53% in comparison to baseline. Similarly, the 24 hour AUC of 4-oxo-isotretinoin increased by 171 + 77% in comparison to baseline. (Chen et al., 1996).

The presence of endogenous all-trans-retinoic acid, 13-cis-retinoic acid, all-trans-4-oxo-retinoic acid and 13-cis-4-oxoretinoic acid as well as the influence of a single dose of vitamin A on retinoic acid levels in human plasma was investigated. Mean plasma concentrations of vitamin A metabolites identified in 10 male volunteers were all-trans-retinoic acid (1.32 ± 0.46 ng/ml), 13-cis-retinoic acid (1.63 ± 0.85 ng/ml) and 13-cis-4-oxoretinoic acid (3.68 ± 0.99 ng/ml). After a single oral dose with vitamin A (833 IU/kg body weight) in 5 male volunteers, mean plasma all-trans-retinoic acid increased to 3.92 ± 1.40 ng/ml and 13-cis-retinoic acid increased to 9.75 ± 2.18 ng/ml. Maximal plasma 13-cis-4-oxoretioic acid concentrations (average 7.60 ± 1.45 ng/ml)

were observed 6 h after dosing which was the last time point in this study. Concentrations of all-trans-4-oxoretinoic acid were low or not detectable (Eckhoff and Nau, 1990b).

Another study investigated the pharmacokinetics of retinol palmitate in ten healthy female volunteers (aged 22-43 years old). The cross over study had a 4 week wash out period between each treatment. Subject received 50 and 150 mg of retinol orally through a supplement, 50 and 150 mg of retinol through calf liver, and 3, 9, and 30 mg through intra-muscular injection. Plasma was analyzed using high performance liquid chromatographic technique. Results demonstrated that retinyl palmitates plasma concentration is higher after oral treatment of 50 mg of retinol in comparison to 50 mg provided in fried calf liver. No significant changes were found for 150 mg treatments. Furthermore, C_{max} and AUC of all-trans-retinoic acid was found to be 20 times more in the group receiving Vitamin A supplements in contrast to the liver group. Other metabolites (13-cis-retinoic acid and 13-cis-4-oxo-retinoic acid) had less marginal variations for liver and supplemental intake. Results from intramuscular treatment of 30 mg of retinol caused increases in retinyl palmitate similar to that of oral doses, however, did not increase concentrations of the acid metabolites (Buss *et al*., 1994).

TOXICOLOGY

Single Dose Toxicity

Single oral doses of the retinoids are considered to have a relatively low order of acute toxicity. In single acute oral dose toxicology studies in mice and rats, the LD_{50} for Vitamin A palmitate 6,060 and 7,910 mg/kg. respectively. Similarly, other forms of Vitamin A have LD_{50} values in a comparable range and, overall, there are little or no differences between species in the acute toxicity of the retinoids to mice and rats (data summarized in Kamm, 1982).

Repeat Dose Toxicity

Subchronic Toxicity

The results of a short-term 16-day oral (gavage) repeat dose toxicology study of Vitamin A palmitate in rats at dose levels of 0, 188, and 283 mg/kg/day was summarized by Kamm (1982). In this study, Vitamin A was described as having effects that were dose-related with regard to incidence, onset and severity; similar effects were observed in 14-day studies of Vitamin A acetate at similar dose levels of up to 300 mg/kg/day in rats and 160 mg/kg/day in dogs, indicating that these forms of Vitamin A provided a comparable spectrum of effects. Across the studies, typical clinical signs of toxicity included: decreased food consumption and decreased body weight gain, erythema, alopecia, mucosal changes, and long bone fracture, as indicated by limping or an altered gait. Alterations in serum clinical chemistry values included elevations in alkaline phosphatase activity and in triglyceride concentration and, less frequently, elevations in transaminase activity. Gross anatomic findings at autopsy often included one or more of the following: evidence of bone fracture, pale and/or mottled liver, increased liver weight, and decreased testicular weight. Histopathologic findings generally consisted of evidence of bone changes and decreased spermatogenesis (Kamm, 1982).

Chronic Toxicity

Longer-duration oral repeat-dose toxicity studies include two 10-month studies in rats and dogs (unpublished data described in FASEB, 1980 and in CIR, 1987). Groups of 10 rats were dosed by oral gavage at levels ranging from 10,000 to 50,000 IU retinyl palmitate/kg body weight/day [reported to be dose levels of 0 (control), 5.5, 13.8, or 27.5 mg /kg/day] for 5 days per week (doses). Groups of 3 dogs were orally dosed (capsules) 5 days a week at levels of approximately 1,000 to 25,000 IU retinyl palmitate/kg/day [reported to be dose levels of (control), 0.6, 2.8, or 13.8 mg /kg /day]. The high dose level in the dogs was approximately 250 times higher than the recommended human allowance for retinyl palmitate (approximately 100 IU or 0.06 mg/kg/day at the time of study conduct). No adverse effects were observed in either species, including no clinical signs of toxicity, no change in weekly body weights, and no hematological findings. No gross or microscopic examination of tissues was performed.

In two additional 10-month toxicity studies with vitamin A palmitate, rats were administered dose levels of 0.06, 0.14, or 0.28 mg/kg/day by oral gavage and dogs were orally dosed at levels of 0, 0.006, 0.03, or 0.15 mg/kg/day (capsule formulation) (Kamm, 1982). The doses were chosen as multiples of the maximum tolerated human dose of 25,000 IU/ kg/day, or approximately 0.15 mg/kg/day at the time of study conduct. No adverse effects were reported in either rats or dogs with respect to mortality, growth, or hematologic parameters such as total red blood cells, total and differential leukocytes, hemoglobin concentration, or prothrombin time. No gross or microscopic examination of tissues was performed.

Other Toxicity Studies

The effects of Vitamin A have been explored in investigative studies in specific organs and tissues:

- While repeated dosing with Vitamin A is known to cause fragile bones, additional investigations were conducted in mature female rats following oral dosing at levels of 120 and 600 IU/g pelleted diet (10- and 50-times the level of Vitamin A in the control diet, respectively). Increases of up to 20-fold normal serum levels of retinyl esters confirmed the intake of Vitamin A. After 12 weeks of dosing, bone diameter was decreased but bone mineral density was unchanged (Lind *et al.,* 2006).

- In an investigative study of effects of retinyl palmitate on brain function, middle-aged rats received oral gavage doses of 0, 300, 600, or 3,000 µg of retinal activity equivalents/kg/day (human equivalent doses of 5, 10, and 50 µg of retinal activity equivalents/kg/day) for 28 days (Schnorr *et al*., 2015). These dose levels were similar to those available in dietary supplements. Retinyl palmitate-dosed rats showed decreases in exploratory behavior and increases in anxiety-related behavior, but not in locomotor activity. These changes were associated with evidence of pro-oxidant events in the brain and not to hepatotoxicity.

- Oral (gavage) dosing of male rats at levels of 0, 1,000, 2,500, 4,500, or 9,000 IU retinyl palmitate/kg/day daily for 3 or 7 days showed evidence of changes in redox indicators such as liver peroxidation, superoxide dismutase (SOD), and catalase (CAT) activities

(increases of 1.2 to 1.7-fold depending on the duration of dosing and the dose level) (de Oliveira *et al*., 2009). The dose levels tested are approximately equivalent to 550, 1,375, 2,475, and 4,950 µg/kg/day.

- Increased risk of hepatotoxicity was associated with increased Vitamin A intake in mice administered intraperitoneal doses of 0 (control) or 500 IU/kg/day for 2 weeks or for 3 weeks (Ibrahim and Okdah, 2015). Findings included congestion and dilation of blood vessels, leucocytic infiltrations, cytoplasmic vacuolation of hepatocytes and fatty degeneration, in addition to elevated liver transaminase and alkaline phosphatase levels in the serum; changes were more severe after 3 weeks of dosing compared to 2 weeks.

- In a 28-day oral gavage study in rats at levels of 0, 1,000, 2,500, 4,500, or 9,000 IU/kg/day, analysis of heart tissues showed increased lipid and protein oxidation, changes in SOD and CAT activities and increases in mitochondrial 3-nitrotyrosine content, suggesting possible oxidative/nitrosative stress (da Rocha *et al*., 2010). The dose levels tested are approximately equivalent to 550, 1,375, 2,475, and 4,950 µg/kg/day.

- In a 12-month study, mice (from 4 weeks of age) were dosed with 20 (control diet) or 200 IU retinyl palmitate/g diet (11 or 110 µg/g diet) to evaluate effects on the heart, including at the tissue and subcellular levels (Huk *et al*., 2013). Mice developed aortic valve stenosis and leaflet calcification, indicating a possible pathway for cardiac disease.

Mutagenicity and Carcinogenicity

The mutagenic and genotoxic potential of vitamin A has been evaluated in several studies. Vitamin A was negative for mutagenicity in an *in vitro* bacterial reverse mutation test at concentrations up to 2.0 mg/plate (as retinaldehyde; full range of concentrations unknown) (Kamm, 1982) and in mouse lymphoma L5178Y/Tk$^{+/-}$ assays [retinyl palmitate at 25 to 100 µg/mL (Mei *et al.,* 2005); retinol at 5 or 10 µg/mL (Mei *et al.,* 2010)]. Retinyl palmitate (20 to 40 µg/mL) was negative for genotoxicity in an *in vitro* chromosomal aberration assay conducted in Chinese Hamster Ovary cells (Dufour *et al*., 2009) and retinol (tested at up to 16 ug/mL) was negative in a sister chromatid exchange assay (Huang *et al*., 1982). Notably, a number of studies have investigated the potential for an inhibitory effect of Vitamin A on mutagenesis induced by other compounds (early studies have been summarized in CIR, 1987).

Early-published reviews of Vitamin A indicated there were no carcinogenicity studies (FASEB, 1980; CIR, 1987) and there was no indication of carcinogenic potential based on concurrent reviews [*e.g.*, status of Vitamin A as Generally Recognized as Safe (CIR, 1987)].

Reproductive and Developmental Toxicology

Fertility and Reproduction

Vitamin A at high doses was shown to have negative effects on sperm motility and survival (single doses of 60,000 to 90,000 IU/kg, intramuscular), as studied in male rabbits (summarized in FASEB, 1980). Retinyl palmitate (5,000 IU, oral, 3 times per week for 9 months, a dose

approximately equivalent to 13,750 µg/kg for a 200 g animal) was shown to have an inhibitory effect on cyclic ovulation in rats (summarized in FASEB, 1980).

Teratogenicity

The teratogenicity of excess vitamin A in laboratory animals is well known and was first reported in the 1950's (see Geelen, 1979), with numerous investigations and reviews, both nonclinical and clinical, in the subsequent decades [FASEB, 1980; Kamm, 1982; CIR, 1987; Hathcock *et al.*, 1990; Ross *et al.*, 2000]. Embryo-fetal effects of Vitamin A and related retinoid compounds are dependent on the stage of gestation, the type of retinoid, and dose level (reviewed in Ross *et al.*, 2000). A "retinoid malformation syndrome" has been described that involves changes to the external ear, craniofacial region, brain, thymus, and heart, as seen in both humans and monkeys (Hendrickx *et al.*, 2000).

In an early study, pregnant rats fed 35,000 IU vitamin A/day (175,000 IU/kg/day) on gestation days 3-16 reduced numbers of litters carried to full term and reduced litter size. Treated dams had an increased incidence of fetal anomalies such as exencephaly, cleft lip and/or palate, brachygnathia, and various eye defects (Cohlan, 1953). Similar teratogenic effects of excess Vitamin A were found in other animal species including mice, guinea pigs, hamsters, monkeys, and rabbits (reviewed in FASEB, 1980). In a later study, rats were dosed by oral gavage with retinyl palmitate 3.2, 32, or 128 mg/kg/day on gestation days 6 to 15 (Hayes *et al.*, 1981). Maternal toxicity, increased fetal resorption, and malformations were observed at 128 mg/kg/day, but there was no teratogenicity or embryolethality at 3.2 and 32 mg/kg/day. Fetuses showed malformations of the craniofacial area. In a different set of studies, Vitamin A palmitate was evaluated in oral studies at dose levels of 0, 5, 15, and 50 mg/kg/day in mice (gestation days 6 to 15), dose levels of 0, 10, 30, and 90 mg/kg/day in rats (gestation days 6 to 15), and dose levels of 0, 0.5, 2, and 5 mg/kg/day in rabbits (gestation days 6 to 18) (Kamm, 1982). In these studies, no-effect levels were identified (15, 30, and 2 mg/kg/day in mice, rats, and rabbits, respectively).

More recently, retinyl palmitate was evaluated for the timing of its effects on limb morphogenesis in mice by the intraperitoneal (ip) injection of 1 or 2 doses on a single day (gestation days 9, 10, 11, or 12) (Rezaei *et al.*, 2009). The ip injections were either 10,000 or 15,000 IU/kg once or twice on a given gestational day, providing doses of 0, 15,000, 20,000, or 30,000 IU/kg per day to pregnant mice. Embryo resorption occurred, and embryos with limb abnormalities were observed in at both dose levels, with the type of malformation varying depending on the gestational day.

The embryo-fetal development effects of Vitamin A were evaluated in cynomolgus monkeys . Vitamin A palmitate was orally administered at 7,500 IU/kg (2.25 mg/kg) to 80,000 IU/kg (24 mg/kg) body weight once daily on gestation days 16 to 27. In the two highest dose groups (40,000 and 80,000 IU/kg/day), there were mild to severe signs of hypervitaminosis A (erythema, skin rash, epistaxis, rhinorrhea, swollen eyelids, gingivitis, lip lesions, and alopecia); fetal effects including malformations and abortions were observed in these groups. There was a dose-related increase in abortion and malformation that affected typical retinoid target tissues in the embryo, including the craniofacial region, heart, and thymus. The results also showed there

was a dose-related increase in exposure (AUC) to retinyl esters and retinoic acids (RA) (all-*trans*-RA, all-*trans*-4-oxo-RA, 13-cis-RA, 13-cis-4-oxo-RA). The NOAEL and LOAEL for structural malformations were 7,500 IU/kg and 20,000 IU/kg (6 mg/kg), respectively. The monkey NOAEL for Vitamin A (7,500 IU/kg) was used to estimate safe levels of this nutrient in humans applying a safety factor of 10. Based on this calculation, the study results indicated safe levels of Vitamin A during human pregnancy would be in the range of 25,000 to 37,000 IU/day (Hendrickx *et al*., 2000).

Exposure to high doses of Vitamin A during specific days of gestation may have long-term effects on the learning and behaviour of offspring, or on their response rates, as reviewed in FASEB (1980).

Peri-/Post Natal Development and Juvenile Animal Studies

Vitamin A was shown to reduce brain weight, free cholesterol, phosphatidal ethanolamine, and synthesis of myelin sulfatides from Na_2SO_4 in a study in rat pups administered 1,000 IU Vitamin A on the 4^{th}, 6^{th}, 8^{th}, and 10^{th} days of age (Joshi *et al.,*, 1983).

Vitamin A supplementation during gestation and for 21 days during lactation resulted in an increase in markers of oxidative damage in the reproductive tissues and plasma of the dams (Schnorr *et al.*, 2011a). Vitamin A (provided as retinol palmitate) was administered by oral gavage at dose levels of 2,500, 12,500, or 25,000 IU/kg/day. Pups of the treated dams showed a decreased potential for antioxidant response in the liver and kidney (decreased superoxide dismutase/catalase activity ratio). These changes were considered to have potential to cause adverse effects in the developing offspring.

High doses of Vitamin A (2,500, 12,500, or 25,000 IU/kg/day) administered during gestation and for 21 days during lactation increased signs of oxidative damage in maternal and offspring striatum and hippocampus (Schnorr *et al*., 2011b). Associated with this were changes in offspring behavior in homing tests performed on post-natal days 5 and 10 and in open field tests on post-natal days 19 and 20, such as decreases in certain behaviours (numbers of crossings, center entries, and rearings, and groomings).

Vitamin A supplementation (providing 216 mg retinyl palmitate/kg of supplemented diet) during lactation (to dams from day of delivery to day 21) and after weaning (to pups) resulted in an altered immune response to an allergen (ovalbumin) injected at day 28 after birth (Rühl *et al*., 2007). Vitamin A intake was confirmed in the serum retinol concentrations that were increased approximately 40 times in treated animals compared to control diet. Compared to basal diet, Vitamin A decreased CD3+, CD4+, CD8+, and B220+ cell populations in splenic lymphocytes and enhanced Interleukin-4 production as well as ovalbumin-specific IgE antibodies, indicating that allergic sensitization is influenced by Vitamin A content in the diet.

The effects of Vitamin A on sexual maturation was investigated in young female rats, comparing adequate levels of Vitamin A in the diet, 5.5-fold increased levels of Vitamin A from fruits and vegetables (*i.e.*, 23,750 IU/kg diet), and 6.2-fold increased levels of Vitamin A as retinyl palmitate (26,790 IU/kg diet) (McDaniel *et al*, 2007). Animals were dosed from post-natal days

21 to 63. There were no effects on body weight. Pubertal rats dosed with retinyl palmitate showed no effects on time of sexual maturation (assessed as onset of vaginal opening), although rats dosed with high Vitamin A levels from fruits and vegetables showed a delay. There was no effect on estrous cycles (cycle number, length, duration of different phases). Mammary gland alveolar development showed signs of inhibition by high dietary Vitamin A levels, with the fruit and vegetable-sourced Vitamin A diet having a greater inhibitory effect compared to the retinyl palmitate diet. Both Vitamin A diets reduced the multiplicity of mammary gland tumours caused by a single injection of the carcinogen 1-methyl-1-nitrosourea at Day 66.

In summary, it appears that the lowest reported adverse effect level in animals is about 30,000 IU/kg/day for periods of 3 to 5 weeks (FASEB, 1980).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation
Vitamin A and Vitamin E Softgel Capsules
Vitamin A (all-trans-retinyl palmitate) and Vitamin E (all-rac-alpha-tocopheryl acetate)

Read this carefully before your child is given **Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation as a softgel capsule**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your child's medical condition and treatment and ask if there is any new information about **Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation**.

What is Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation used for?
Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation is intended to be used only in young children who are 6 months to 11 months of age to prevent symptoms of Vitamin A deficiency (or VAD). These symptoms can include night blindness, buildup of a protein called keratin in the eye (known as Bitot's spots, they appear as irregular foamy shapes on the eye) and dry eyes (known as xerophthalmia).

The World Health Organization recommends Vitamin A treatment in places where VAD is a public health problem as follows:

- When night blindness occurs in 1% or greater in children who are 24 to 59 months of age, or
- Where VAD (which is measured in the blood as serum retinol 0.70 μmol/L or lower) occurs in 20% or higher in children who are 6 to 59 months of age.

How does Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation work?
Vitamin A is a co-factor in many biological processes in the body, including those responsible for good vision.

What are the ingredients in Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation?
Medicinal Ingredients:
Vitamin A (all-trans-retinyl palmitate) and Vitamin E (all-rac-alpha-tocopheryl acetate)

Non-medicinal Ingredients:
D&C red #28, ethyl vanillin, FD&C blue #1, gelatin, glycerin, soy bean oil, titanium dioxide. May contain trace levels of lecithin.

Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation comes in the following dosage forms:
Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation will be provided as a blue tube shaped softgel capsule with a nipple tip to allow for cutting and squeezing out the drops for a one time dose.

The softgel capsules are packaged in plastic bottles. Each bottle contains 500 softgel capsules.

Do not use Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation if:

- Your child is younger than 6 months of age
- You are not in an area where vitamin A deficiency is a public health concern
- You or your child are allergic to any of the ingredients in Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation
- You or your child have symptoms of having too much Vitamin A in the body, such as; changes in vision, bone pain, and skin changes (known as hypervitaminosis A)
- You are pregnant or want to become pregnant, because high doses of vitamin A have caused birth defects.

This product is only meant to be given to children who are 6 months of age to 11 months of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation is given to your child. Talk about any health conditions or problems your child may have, including if:

- Your child has a cold or flu (respiratory infections)
- Your child requires a vaccine, especially measles vaccine and diphtheria-tetanus pertussis (DTP) vaccine
- You are breastfeeding, as additional vitamin A can be excreted in human breast milk and passed to your infant.

Other warnings you should know about:
There are many different vitamins in your child's normal diet. If your child has a deficiency in his/her diet, there would probably be a lack multiple vitamins, not just lack Vitamin A.

High doses of Vitamin A should only be given to children in areas where there is known deficiency of Vitamin A.

Take special care to avoid accidental exposure of your child to multiple large doses over a short period of time. The long term effect of high doses of Vitamin A in children (especially on the effects on their bones) has not been studied.

Take special care if your child has a chest (or respiratory) infection before you give Vitamin A.

Tell your healthcare professional about all the medicines you or your child are taking, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation:

- Diphtheria-tetanus-pertussis (DTP) vaccine: There is potential interaction between Vitamin A supplementation and vaccination; children should never be given high doses of Vitamin A with DTP vaccine.

- Measles vaccination: Giving Vitamin A with the measles vaccine may cause vomiting, loose stools, fever and irritability within 24 hours of receiving the vaccine.
- Calcium: Taking large doses of Vitamin A for long periods of time can cause bone loss.
- Vitamin D: Vitamin A may affect the action of Vitamin D.
- Vitamin E: Large doses of Vitamin E can affect the absorption of Vitamin A.
- Zinc: Lack of zinc may affect the breakdown of Vitamin A in the body.

Vitamin A may interact with other nutrients; these effects have not been studied and may not be fully known.

How to take Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation:

- Cut capsule end.
- Squeeze drops into child's mouth until the capsule is empty.
- Do not put the capsule into your child's mouth or let them swallow it.

Usual dose:
Your healthcare professional will recommend a single dose of Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation for your child who is 6 months to 11 months of age. The dose will be given by a healthcare professional.

If your child is 12 months to 59 months of age, you should refer to the Patient Medication Information for a different medication, **Vitamin A (200,000 IU) and Vitamin E (40 IU)** which is given every 4 to 6 months instead.

Overdose:
Do not give your child more than 1 dose. Signs and effects of overdose may be delayed and may not show until 8 to 24 hours after taking the medication. These side effects can include; feeling sick, vomiting, diarrhea, changes in behavior, and skin changes (itching of the skin, redness, or peeling).

If you think you have taken too much Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Your child will be given only 1 dose.

What are possible side effects from using Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation?
Most common side effects are mild and may include skeletal abnormalities, bone tenderness and pain, increased intracranial pressure, peeling skin, brittle nails, mouth fissures, hair loss, fever, headache, lethargy, irritability, weight loss, vomiting, swollen liver, loose stools, headache, irritability, and feeling sick. These side effects usually disappear within 24 to 48 hours after giving Vitamin A.

These are not all the possible side effects that your child may have after taking Vitamin A

(100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation. If your child has any troublesome side effect not listed here, or affects their usual daily activities, contact your healthcare professional. Please also see Warnings and Precautions.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

You can also contact your **local health authority** or the **World Health Organization (WHO)** to report a serious and unexpected side effect.

Storage:
Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation
The container is kept tightly closed, protected from moisture and light, in a cool, dry place. Temperatures above 30°C and high humidity should be avoided.

Keep out of reach and sight of children.

If you want more information about Vitamin A (100,000 IU) and Vitamin E (20 IU) Oral Liquid Preparation

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.nutricorp.com or by calling Nutricorp International, 1-888-446-8874.

This leaflet was prepared by Nutricorp International.

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