1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

OLPHARM VITAMIN A 200000 IU

1. Product Name:
Trade name: Olpharm Vitamin A 200000 IU
Generic name: vitamin A Capsules 200000 IU

2. Label claim:
Each soft gelatin capsule contains
Vitamin A USP (as palmitate) 200000 IU

3. Qualitative and Quantitative formula

Batch size 100000 capsules
Description: Reddish Orange colored, Oval shaped, transparent, softgelatin capsules containing yellow coloured oily liquid

S. No	Ingredients	Specification	Overages %	Qty per capsule (mg)	Qty per batch (kg)	Therapeutic category
Fill material *						
1.	Vitamin A (as palmitate)	USP	17%	137.64	13.764	Nutritional supplement
2.	Refined Soya oil	BP	Nil	122.16	12.216	Solvent
3.	Butylated Hydroxy anisole	BP	Nil	0.1	0.01	Antioxidant
4.	Butylated Hydroxy toluene	BP	Nil	0.1	0.01	Antioxidant
Shell materials **						
5.	Gelatin	BP	Nil	82.516	8.2516	Gelling agent
6.	Glycerol	BP	Nil	21.979	2.1979	Antimicrobial preservative
7.	Liquid sorbitol (Non-crystallizing)	BP	Nil	10.99	1.099	Diluent
8.	Methyl hydroxy benzoate	BP	Nil	0.495	0.0495	Antimicrobial preservative
9.	Propyl hydroxy benzoate	BP	Nil	0.049	0.0049	Antimicrobial preservative
10.	Ponceau 4R	IH	Nil	0.146	0.0146	Coloring agent
11.	Purified water	BP	Nil	15.825	1.5825	Solvent

** addition to the batch quantity for gelatin mass formula extra quantity will be taken during manufacturing to compensate manufacturing loss in various stages

Abbreviation :
BP: British pharmacopeia
IHS: in house specification

OLPHARM VITAMIN A 200000 IU

USP: united states pharmacopeia

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light. Vitamin A deficiency when the dietary intake is inadequate and is seen more frequently in young children than in adults. It is rare in developed countries but remains a major problem in developing countries. Prolonged deficiency leads to xeropthalmia or "dry eye", the initial symptom of which may progress to severe eye lesions and blindness. Other symptoms include changes in the skin and mucous membranes.

Vitamin A has also been used alone to treat various skin disorders including acne and psoriasis. It has been tried in patients with retinitis pigmentosa to retard the decline in retinal function.

In Anaemia: there has been a study among pregnant women with nutritional anaemia that demonstrated a beneficial effect of Vitamin A on haemoglobin when given with iron supplementation.

Diarrhoea: several of the large mortality trials already mentioned reported that Vitamin A supplementation was associated with reduced mortality attributed to diarrhoea, but did not.

Measles: Vitamin A supplementation has an important role in the prevention of complications from measles. Two studies specially addressing vitamin A status and measles had found that complications such as pneumonia and diarrhoea were less common in children who had received supplement at the time of diagnosis than in those given a placebo. Meta-analysis of randomised trials concluded that a dose 200 000 units of vitamin A given on two consecutive says duced mortality in children with measles. WHO has recommended treating children in populations where vitamin A deficiency is common with high-dose vitamin A supplement during episodes of measles. A dose of 200 000 units should given on two consecutive days to all children over 12 months of age. This should be followed by a further dose at least weeks later. Infants less than 6 months of age should receive doses of 50 000 units and those between 6 and 12 months should be given 100 000 units. Studies in the USA have indicated that even among well-nourished children from a developed country. Vitamin A deficiency in measles patients is in uncommon, and Vitamin A supplementation needs to consider in children risk.

Shigellosis: A single high __ dose vitamin A supplement reduces the severity of acute shigellosis in children.

Xeropthalmia: Vitamin A deficiency is responsible is man developing countries for visual problems which may culminat in xerophthalmia and blindness. Supplementation with vitamin A as recommended by status of the individual and act prophylactically against the development of xerophthalmia. For the treatment xerophthalmia (which includes night blindness, conjunctival xerosis with Bitot 's spots, corneal xerosis, corneal ulceration, and keratomalacia) WHO have stated that oral doses of vitamin A , are the treatment t of choir and should be given immediately the disorder is recognized.

Reference: Martindale. Thirty third edition.pg.no.1382-1383.

4.2 Posology and method of administration

Oral route.

Dosage:

Treatment:

A schedule of three doses of oral Vitamin A: immediately on diagnosis, following day and between 7 days and 4 weeks

Adults and children over 1 year	200,000 IU
Children between 6 months and 1 year	100,000 IU

Infants under 6 months	50,000 IU
Mother:	20,000 IU starting at time of delivery.
Prevention:	
Adults and children over 1 year	200,000 IU every 3 to 6 months
Children between 6 months and 1 year	100,000 IU every 3 to 6 months
Infants under 6 months	50,000 IU

(Do not use if the mother of a breast fed infant has received a supplemental dose)

Mother: 200,000 IU at time of delivery,
Or in the two months which follow.

Reference: Martindale. Thirty third edition.pg.no.1382-1383.

4.3 Contraindications

Hypersensitivity to vitamin A, chronic alcohol abuse; liver diseases; chronic renal failure and malignant neoplasm. Use in patients with a known hypersensitivity to Vitamin E.

Reference: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6179

4.4 Special warnings and precautions for use

Avoid overdosage. Keep out of the reach of children.

Pediatric Use:

Polysorbates have been associated with E-Ferol syndrome (thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis) in low birth weight infants.

General use:

Protect from light. Prolonged daily dose administration over 25,000 Units vitamin A should be under close supervision. Blood level assays are not a direct measure of liver storage. Liver storage should be adequate before discontinuing therapy. Single vitamin A deficiency is rare. Multiple vitamin deficiency is expected in any dietary deficiency.

Reference: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6179

4.5 Interaction with other medicinal products and other forms of interaction

Absorption of vitamin A from the gastrointestinal tract may be reduced by the presence of neomycin, colestyramine, or liquid paraffin.

There is an increased risk of hypervitaminosis A if vitamin A is coadministered with synthetic retinoids such as acitretin, isotretinoin and tretinoin.

There is conflicting evidence regarding the effect of vitamin A on the response to measles vaccine.

Reference: Martindale. Thirty third edition.pg.no.1382-1383.

4.6 Pregnancy and lactation

High doses of Vitamin A should not be used in (possible) pregnancy, because of potential teratogenic effects.

Weekly doses not exceeding 25,000 IU are regarded to be safe.

Possible risk of toxicity in breast feeding child at weekly doses exceeding 25,000 IU.

Reference: Martindale. Thirty third edition.pg.no.1382-1383.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

The administration of excessive amounts of vitamin A substances over long periods can lead to toxicity known as hypervitaminosis A. This is characterized by fatigue, irritability, anorexia and loss of weight, vomiting and other gastrointestinal disturbances, low grade fever, hepatosplenomegaly, skin changes (yellowing dryness sensitivity to sunlight), alopecia, dry hair cracking and bleeding lips, anaemia headache , hypercalcaemia, subcutaneous swelling, nocturia and pains in bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, tinnitus and visual disturbances which may be severe. Symptoms usually clear on withdrawal of vitamin A, but in children premature closure of the epiphyses of the long bones may results in arrested bone growth.

Acute vitamin A intoxication may occur with very high doses and is characterized by sedation, dizziness, nausea and vomiting, erythema, pruritus, desquamation and increased intracranial pressure (resulting in bulging fontanelle in infants).

Hypervitaminosis A does not appear to be problem with large doses of carotenoids. Enchanced susceptibility to the effects of vitamin A may be seen in children and in patients with liver disease. Excessive doses of vitamin A should be avoided in pregnancy because of potential teratogenic effects.

Gastrointestinal absorption of vitamin A may impaired in cholestatic jaundice and fat-malabsorption conditions.

Reference: Martindale. Thirty third edition.pg.no.1382-1383.

4.9 OVERDOSE

Symptoms of overdose may include: severe headache, tiredness, dizziness, mental/mood changes (such as irritability, depression), vision changes (such as double vision, blurred vision), dry/peeling skin, bone/joint pain, loss of appetite, yellowing skin/eyes, dark urine, severe stomach/abdominal pain.

Reference: http://www.webmd.com/drugs/drug-10902-Vitamin+A+Palmitate+Oral.aspx?drugid=10902&drugname=Vitamin+A+Palmitate+Oral&source=3#sideeffects

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Beta-carotene, retinol, and retinal have effective and reliable vitamin A activity. Retinal and retinol are in chemical equilibrium in the body and have equivalent antixerophthalmic activity. Retinal combines with the rod pigment, opsin, in the retina to form rhodopsin, necessary for visual dark adaptation. Vitamin A prevents retardation of growth and preserves the epithelial cells' integrity. Normal adult liver storage is sufficient to satisfy two years' requirements of vitamin A.

Vitamin A is readily absorbed from the gastrointestinal tract, where the biosynthesis of vitamin A from beta-carotene takes place. Vitamin A absorption requires bile salts, pancreatic lipase, and dietary fat. It is transported in the blood to the liver by the chylomicron fraction of the lymph. Vitamin A is stored in Kupffer cells of the liver mainly as the palmitate.

Reference: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6179

5.2 Pharmacokinetic properties

Vitamin A substances are readily absorbed in the gastrointestinal tract but absorption may be reduced in the presence of fat malabsorption, low protein intake or impaired liver or pancreatic enzymes to retinol, which is then absorbed and re-esterified. Some retinol is stored in the liver. It is released from the liver bound to a specific α_1-globulin (retinol-blinding protein) in the blood. The retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid; these and other metabolites are excreted in urine and feaces. Vitamin A does not readily diffuse across the placenta but is present in breast milk.
Reference: Martindale. Thirty third edition.pg.no.1382-1383.

5.3 Preclinical safety data
Vitamin A is obtained from the diet in the form of retinyl esters, which are subsequently de-esterified to retinol. Retinol is then irreversibly oxidized to become retinoic acid. Retinoic acid is the form of vitamin A that binds with nuclear receptor sites and is necessary for the normal growth and differentiation of epithelial tissue.

The effects of vitamin A on cellular differentiation are mediated by two separate classes of nuclear receptors, which in turn modify the effects of many compounds, including prostaglandins, vitamin D, and steroid and thyroid hormones. Many studies have examined the effects of isomers of vitamin A, including all-trans retinoic acid, 9-cis retinoic acid, and 13-cis retinoic acid. These isomers are all considered to be interconverted in humans, and may be less hepatotoxic than retinol.
Animal research has demonstrated a chemo preventive effect of retinoids in many types of cancer, including mammary cancer and colon cancer models. In vitro research has identified a number of promising mechanisms of action, including decreasing serum insulin-like growth factor-1, inhibition of 5-alpha-reductase (the enzyme that catalyzes formation of dihydrotestosterone), and up-regulation of transforming growth factor-beta.
Epidemiological studies on the cancer preventive activity of dietary vitamin A have been inconclusive, perhaps because of confounding factors. Vitamin A is only present in animal foods, and thus dietary vitamin A intake may be a marker for a high meat diet, a risk factor for many cancers. Prospective trials have shown a very modest reduction in breast cancer risk in women with the highest intakes of dietary vitamin A. One prospective epidemiological trial concluded that people taking supplemental vitamin A had a reduced risk of developing breast cancer only if they were in the lowest third of dietary vitamin A intake. Although the preclinical data have been promising, human studies using vitamin A or retinoids as chemo preventive agents have been largely disappointing. It appears likely from the epidemiological data that the protective effect of retinoids is limited to those who are deficient in dietary vitamin A. It is also possible that the effect is limited to particular clinical situations (e.g., bladder cancer, premenopausal breast cancer).
Reference: http://www.chiro.org/nutrition/ABSTRACTS/Natural_Agents_in_Prevention_PART_2.shtml

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S.No	INGREDIENTS	SPECIFICATION
1	Refined Soya Oil	BP
2	Gelatin	BP
3	Glycerol	BP
4	Liquid sorbitol	BP
5	Methyl hydroxy benzoate	BP
6	Propyl hydroxy benzoate	BP
9	Ponceau 4 R	In-House
10	Purified water	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Vitamin A and its esters are sensitive to the action of air, oxidising agents, acids, light, and heat. Store in well-filled airtight containers. Protect from light. Once the container opened, its contents should be uses as soon as possible and any part of the contents not used should be protected by an atmosphere of inert gas.

6.5 Nature and contents of container

Vitamin A CAPSULES 200000 IU are available in 3x10 blister pack