# SUMMARY OF PRODUCT CHARACTERISTICS

**Unofficial translation of the German SmPC. This translation is provided as an aid for non-German speaking readers. Please refer to the official German SmPC in case of doubt.**
**Of note, KA-VIT® Tropfen is not approved outside Germany.**

## 1. NAME OF THE MEDICINAL PRODUCT

**KA-VIT® Tropfen**
**(KA-VIT® Drops)**
20 mg/ml Oral emulsion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: phytomenadione (vitamin $K_1$)

1 ml oral emulsion (20 drops) contains 20 mg phytomenadione (vitamin $K_1$).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Clear or slightly opalescent, yellow oral emulsion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

The only approved therapeutic indications for KA-VIT Drops are the therapy of vitamin K deficiency conditions and the prevention of vitamin K deficiency conditions that cannot be resolved by nutrition. These include:

- Vitamin K prophylaxis in neonates immediately after birth
- Vitamin K prophylaxis in patients with risk factors for the development of vitamin K deficiency, as soon as the Quick's value falls below the limit of normal or the INR rises above the limit of normal, respectively
- Vitamin K treatment in patients with vitamin K deficiency bleeding, which usually involves a Quick's value below 10 % or an INR value above 5, respectively. Vitamin K deficiency bleeding can be caused by a genuine vitamin K deficiency or by an excessive dose of coumarin derivatives.

<u>Indications of risk factors for a vitamin K deficiency</u>
The following are risk factors in neonates and infants:

- Intake of certain drugs (anticonvulsants, antituberculosis drugs and coumarin derivatives) during pregnancy and lactation,
- Premature birth, small-for-date babies, complicated birth, delayed start of feeding, exclusively breast-fed babies and insufficient feeding.

The following are risk factors in infants, older children and adults

- Malabsorption syndromes, parenteral nutrition, cholestasis (biliary atresia, alpha-1-antitrypsin deficiency, cystic fibrosis, cytomegalovirus infection, obstructive jaundice),

- Pancreatopathy, A-β-lipoproteinaemia, antibiotic treatment (particularly cephalosporins), treatment with sulphonamides or salicylates.

Indications of deficiency symptoms
Vitamin K deficiency symptoms can either be precipitated by genuine vitamin K deficiency (e.g. nutritional or absorptive) or by therapeutic administration of coumarin derivatives or various inhibitors of the vitamin $K_1$ epoxide reductase. Clinically, they take the form of haemorrhage symptoms, such as bruising, melaena (tarry stool), haematuria and CNS bleeding.

## 4.2 Posology and method of administration

Posology
Prophylactic administration:
*Healthy neonates of 36 weeks gestation and older*
The recommended dose in healthy neonates of this age group is 2 mg phytomenadione (equivalent to 2 drops of KA-VIT) given orally at birth or soon after birth (U1)[1], followed by a second dose of 2 mg at 3 to 10 days of age (U2)[1]. A further dose of 2 mg should be given 4 to 5 weeks after birth (U3)[1]. In exclusively formula fed infants the third oral dose can be omitted.

*Preterm neonates of less than 36 weeks gestation, and term neonates at special risk (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics)*
One dose of phytomenadione should be administered intramuscularly or intravenously at birth or soon after birth. Other phytomenadione-containing drugs are available for this purpose. KA-VIT is NOT suited for intramuscular or intravenous application.

There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease and malabsorption (see section 5.1).

Therapeutic administration
In patients with vitamin K deficiency bleeding, the dosage should be determined according to effect:
- In cases of mild bleeding, a dose of 1 to 5 mg phytomenadione (equivalent to 1 to 5 drops of KA-VIT) is sufficient for infants and adults.
- In patients with vitamin K deficiency bleeding due to overdose with coumarin derivatives, who have mild bleeding, discontinuation of the anticoagulant is usually sufficient.
- In cases of moderately severe bleeding, a dose of 5 to 10 mg phytomenadione (equivalent to 5 to 10 drops of KA-VIT) will ensure a sufficient increase in the prothrombin complex.

Method of administration
KA-VIT Drops should be taken with some fluid.

Note on laboratory test for vitamin K deficiency
With regard to laboratory diagnosis, a vitamin K deficiency can be assumed if the Quick's value is markedly decreased or the INR value is markedly increased, respectively. It is probably present if the vitamin K-dependent clotting factors II, VII, IX and X are lowered or their inactive decarboxylated precursors (PIVKA) are evident. A vitamin K deficiency is confirmed if these abnormal laboratory values normalise after vitamin K administration (Koller's test).

Occurrence of natural vitamin K sources
Vitamin $K_1$ is mainly found in the green leaves of various types of cabbage, nettles, alfalfa and spinach, as well as in fruits (e.g. tomatoes, strawberries, rose hips) and meat obtained from muscle, liver, milk and eggs. The daily requirement is at least 1 to 2 µg/kg body weight in adults and older children, and approximately 10 to 20 µg/kg BW in infants. The requirement is covered by the daily

[1] U1, U2, U3 correspond to the German equivalent of well-child visits with the attending paediatrician.

diet, e.g. 100 g tomatoes contain up to 400 µg, lettuce contains 700 µg and liver contains 600 µg vitamin $K_1$. The exogenous vitamin K supply is marginal in fully breast-fed infants.

## 4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

In patients controlled on coumarin derivatives who are given KA-VIT Drops to reverse the effect of these compounds, it must be borne in mind that the coagulation properties of the blood change and that the risk of thrombosis can therefore occur, because the clotting factors are more rapidly activated by vitamin $K_1$ than the anti-clotting factors.

## 4.4 Special warnings and precautions for use

No particular precautions or measures are required.

## 4.5 Interaction with other medicinal products and other forms of interaction

KA-VIT Drops reverse the effect of oral anticoagulants.

Coumarin derivatives inhibit epoxide reductase in the vitamin K cycle and thus the cofactor function of vitamin K in the carboxylation reaction.
Acetylsalicylic acid and other salicylates also reduce the effect of vitamin K through inhibition of the carboxylase/reductase system.
Cephalosporins with the N-methylthiotetrazole group inhibit vitamin K epoxide reductase and thus the activity of vitamin K.
Anticonvulsants, such as phenobarbital and diphenylhydantoin (phenytoin), and the antituberculosis drugs isoniazid (INH) and rifampicin can cause vitamin K deficiency bleeding on the first day of life in neonates whose mothers took these drugs during pregnancy.
Chronic use of mineral oils (e.g. liquid paraffin) and concurrent administration of colestyramine or azathioprine impair vitamin $K_1$ absorption.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Vitamin $K_1$ only crosses the placental barrier to a slight extent. To date, experience with vitamin $K_1$ administration in pregnant women at therapeutic doses has not shown any damage to the foetus.

Breast-feeding
Vitamin $K_1$ is excreted into the breast milk.
To date, experience with vitamin $K_1$ administration in breast-feeding women at therapeutic doses has not shown any damage to the child.

## 4.7 Effects on ability to drive and use machines

No particular precautions are required.

## 4.8 Undesirable effects

The following frequency conventions are used in the rating of undesirable effects:

| | |
|---|---|
| Very common | (≥ 1/10) |
| Common | (≥ 1/100 to < 1/10) |
| Uncommon | (≥ 1/1,000 to < 1/100) |
| Rare | (≥ 1/10,000 to < 1/1,000) |

Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

In very rare cases, allergic reactions to the active substance, phytomenadione, have been reported.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, Website: http://www.bfarm.de.

### 4.9 Overdose

To date, no toxic reactions are known, even after extreme overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagic agents, vitamin K

ATC code: B02BA01

Phytomenadione is a fat-soluble vitamin.

Mechanism of action
Vitamin K is active in the microsomes of the hepatocytes as a co-factor of microsomal glutamyl carboxylase. Vitamin K has to be available in its reduced form as hydroquinone and NADPH has to be present in the liver microsomes as a reduction medium. For the carboxylation reaction of the vitamin K-dependent proteins, with the help of the microsomal carboxylase system and in the presence of $O_2$ and $CO_2$, hydroquinone is converted to 2,3-epoxide, which is then reduced by an epoxide reductase to natural vitamin K. Vitamin K antagonists of the coumarin group can inhibit this epoxide reductase.

Pharmacodynamic effects
Through the carboxylation, the vitamin K-dependent proteins can bind calcium ions. The relevant vitamin K-dependent proteins include the clotting factors II, VII, IX and X. The clotting inhibitor proteins C, S and Z are also vitamin K-dependent.

Further vitamin K-dependent but clotting-neutral proteins were also isolated from bones (osteocalcin), teeth, kidneys, liver, placenta and pancreas. Without vitamin K, these proteins occur as inactive decarboxy precursors, previously called PIVKA (protein induced by vitamin K absence or antagonist). The presence of such decarboxy precursors (e.g. of PIVKA II = decarboxy form of prothrombin) is considered to be an important marker of a vitamin K deficiency.

Paediatric population
A prospective randomised controlled study included 44 infants (1–26 weeks of age) with conjugated hyperbilirubinaemia (17 patients with idiopathic neonatal hepatitis, 13 patients with biliary atresia, 3 patients with total parenteral nutrition cholestasis, 2 patients with Alagille's syndrome, 2 patients with alpha-1-antitrypsin deficiency, 2 patients with inspissated bile syndrome, and 5 patients with miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis)). The pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver diseases was compared.

Main outcome measures were serum concentrations of vitamin $K_1$ and decarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar $K_1$ 1 mg intravenously or 2 mg orally. A comparison was also made between vitamin $K_1$ levels at 24 hours after oral administration with those of 14 healthy newborns given the same dose.
Results: At admission, 18 infants (41 %) had elevated levels of serum PIVKA-II and 8 infants (18 %) had low $K_1$ concentrations, indicative of subclinical vitamin K deficiency. Median serum $K_1$ concentrations were similar in the oral and intravenous groups at baseline (0.92 vs 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous $K_1$ administration but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum $K_1$ compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4 out of 24 patients (17 %) achieved an incremental rise in serum $K_1$ > 10 ng/ml.

The data from a retrospective study indicate that weekly oral prophylaxis was effective in the prevention of VKDB. A total of 507,850 live babies were born during the study period, November 1992 to June 2000. Of these infants, 78 % received oral and 22 % intramuscular prophylaxis, respectively; i.e. about 396,000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breast-fed. Oral vitamin $K_1$ prophylaxis at birth of 2 mg followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age. No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100,000 (95 % CI).

## 5.2 Pharmacokinetic properties

Absorption
Vitamin $K_1$ is absorbed from the intestine. Due to its liposolubility, bile acids and pancreatic lipase are required for absorption.

Distribution
In the blood, vitamin $K_1$ is transported in bound form to lipoproteins, mainly to the very low density lipoproteins (VLDL).
In neonates, following oral administration of 1 mg vitamin $K_1$, peak plasma levels of 73 ng/ml were measured after 4 hours. The normal value in adults is approximately 1 ng/ml.
Vitamin $K_1$ mainly accumulates in the liver, and to a lesser extent in the adrenal glands, lung, bone marrow, kidneys and lymph nodes.
Vitamin $K_1$ only crosses the placental barrier to a slight extent.

Elimination
Vitamin $K_1$ is mainly excreted via the bile in the faeces and partially in the urine.

## 5.3 Preclinical safety data

The preclinical data from standard studies on acute toxicity, chronic toxicity and genotoxicity do not indicate any risk potential in humans.
No long-term carcinogenicity studies have been performed.
In animal studies, vitamin $K_1$ has not been adequately investigated for properties relating to reproductive toxicology.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium edetate
Polysorbate 80
Sorbic acid
Purified water

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

18 months (in the unopened container).

Shelf life after opening the dropper bottle: 3 months at room temperature.

Note:
Any slight opacity (opalescence) is caused by the emulsion character of the formulation and does not impair the efficacy of KA-VIT Drops.
The medicinal product may no longer be used if it shows severe opacity and/or a change in the colour of the emulsion to orange-brown.

### 6.4 Special precautions for storage

Do not cool.
Do not store above 25 °C.
Store in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

Original pack containing 1 dropper bottle with 5 ml emulsion,
Original pack containing 1 dropper bottle with 10 ml emulsion,
Original bundle packaging containing 3 x 10 ml emulsion.

### 6.6 Special precautions for disposal

The medicine must not be disposed of via waste water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

If the bottle is held upside down, the emulsion can be administered as drops.

## 7. MARKETING AUTHORISATION HOLDER

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## 8. MARKETING AUTHORISATION NUMBER(S)

3001904.00.00

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18.02.2005

## 10. DATE OF REVISION OF THE TEXT

November 2016

## 11. GENERAL CLASSIFICATION FOR SUPPLY

Pharmacy-only medicinal product