Application for the inclusion of phytomenadione as mixed micelle (MM) solution for intramuscular and intravenous injection or oral administration for children and adults in the WHO Model List of Essential Medicines (EML and EMLc)

Indication in children:

- Prophylaxis and treatment of haemorrhagic disease of the newborn
- Intramuscular, intravenous, or oral use

Indication in adults:

- Haemorrhage or risk of haemorrhage as a result of severe 'hypoprothrombinaemia' (i.e. deficiency of clotting factors II, VII, IX and X) of various aetiologies, including overdosage of coumarin-type anticoagulants, their combination with phenylbutazone and other forms of hypovitaminoses K (e.g. in obstructive jaundice as well as liver and intestinal disorders, and after prolonged treatment with antibiotics, sulphonamides or salicylates)
- Intravenous or oral use

Formulations:

phytomenadione MM paediatric 2 mg/0.2 mL

phytomenadione MM 10 mg/mL

Marketing authorisation holder and applicant:

CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany

Persons to contact:

Dr. Katharina Hill

Email: katharina.hill@cheplapharm.com

Phone: + 49 3834 3914 464

Dr. Karina Grube

Email: karina.grube@cheplapharm.com

Phone: + 49 3834 3914 245

Date of submission:

01 November 2024

1. Summary statement of the proposal

We propose the addition of the phytomenadione mixed micelle solution formulation for intramuscular and intravenous injection or oral administration (phytomenadione MM) to the WHO EML and WHO EMLc in addition to the current phytomenadione formulations of injection and tablets.

Phytomenadione MM is formulated as a binary mixed micelle solution, a combination of micelle-forming glycocholic acid and lecithin, which together forms a physiologically compatible and thermodynamically stable system that can be administered orally and parenterally (intramuscular/intravenous). It is available as a solution in glass ampoules containing either 2 mg/0.2 mL or 10 mg/mL.

Phytomenadione MM (vitamin K1) is indicated for the prophylaxis and treatment of haemorrhagic disease of the newborn and for the treatment of haemorrhage or risk of haemorrhage as a result of severe 'hypoprothrombinaemia' (i.e. deficiency of clotting factors II, VII, IX and X) of various aetiologies (overdosage of coumarin-type anticoagulants and others).

Bleeding complications represent a high risk for patient safety. The severity and outcome of the bleeding is essentially related to the location of the event. Especially patients with intracranial bleeding are exposed to a particularly high risk with a potentially fatal outcome.

When phytomenadione MM was given orally to fully breast-fed newborns, it was absorbed faster than the comparator formulation. The drug was shown to be exceptionally safe and well tolerated and was at least as effective as other oral phytomenadione formulations in bleeding prevention in the newborn. In addition, a single intramuscular injection of phytomenadione MM is a simple, fast and safe alternative for neonatal prophylaxis, especially in world regions with limited health care systems, where there is a risk of incomplete oral prophylaxis.

Further, the available evidence suggests that phytomenadione MM is safer than the comparator formulation when injected intravenously, resulting in a marked decrease in anaphylactic reactions.

According to WHO EML and WHO EMLc, phytomenadione containing tablets are already classified as essential medicine. A significant/major advantage of the MM solution as dosage form is that it can also be administered orally like tablets but allows a more precise and flexible adjustment of the dosage to be administered. Especially for the uncomplicated reintroduction of anticoagulant therapy, it is particularly important to administer only as much of the antidot phytomenadione as necessary to avoid temporary resistance to prothrombin-depressing anticoagulants (vitamin K antagonists). This can be difficult with tablets due to the fixed-dose system, so that excessive dosages could have a negative impact on patient safety. This is not a concern with phytomenadione MM, since any desired dosage can be applied due to the finely adjustable solution. Another important advantage is that it contains a mixed micelle system that acts as its own transport system, whereas in the case of tablets, patients with deficiencies in bile acid production need to be given bile acids additionally. Furthermore, the phytomenadione MM solution can be administered without any concerns when tablets cannot be used for other reasons, e.g. when children or older people have difficulty swallowing.

The importance of phytomenadione MM is reflected in the mention in medical guidelines and textbooks, e.g. in the United Kingdom and Germany phytomenadione MM is recommended for the newborn prophylaxis, and additionally in Germany as an antidot for vitamin K antagonists.

All in all the inclusion of phytomendione MM formulation may provide more flexibility for the administration of this medicine, which will be beneficial to patient treatment.

2. Consultation with WHO technical departments

The submission is made by CHEPLAPHARM Arzneimittel GmbH. There has been a consultation with WHO experts on October 10th, 2024. The following experts were present for consultation at the meeting: Bernadette Cappello, Wilson Milton Were, Ayesha De Costa, Queen Dube, Yuyun Maryuningsih and Lorenzo Moja. Before the meeting a preliminary draft of the application was provided to Mrs. Bernadette Capello.

3. Other organisations(s) consulted and/or supporting the submission

Not applicable, no other organisations were consulted for this application.

4. Key information for the proposed medicine

Table 1. Key information for phytomenadione MM 2 mg/0.2 mL

INN	Phytomenadione		
ATC code	B02BA01		
Indication	Prophylaxis and treatment of haemorrhagic disease of the newborn		
ICD-11 code	KA8F Neonatal vitamin K deficiency		
Dosage form	**Strength**	**EML**	**EMLc**
mixed micelle solution for intramuscular and intravenous injection or oral administration in ampoules	2 mg/0.2 mL	No	Yes
mixed micelle solution for intramuscular and intravenous injection or oral administration in ampoules	10 mg/1 mL	No	Yes

Table 2. Key information for phytomenadione MM 10 mg/1 mL

INN	Phytomenadione		
ATC code	B02BA01		
Indication	Treatment of haemorrhage or risk of haemorrhage as a result of severe hypoprothrombinaemia		
ICD-11 code	3B21 Haemorrhagic disorder due to circulating anticoagulants and coagulation factors		
Dosage form	**Strength**	**EML**	**EMLc**
mixed micelle solution for intramuscular and intravenous injection or oral administration in ampoules	2 mg/0.2 mL	Yes	Yes
mixed micelle solution for intramuscular and intravenous injection or oral administration in ampoules	10 mg/1 mL	Yes	Yes

5. Listing as an individual medicine or as representative of a pharmacological class or therapeutic group ('square box' listing)

We propose the listing of phytomenadione MM as an individual medicine.

6. Information supporting the public health relevance

6.1 Phytomenadione MM paediatric 2 mg/0.2 mL

Phytomenadione MM paediatric 2 mg/0.2 mL is indicated for the prophylaxis and treatment of haemorrhagic disease of the newborn. It contains the active ingredient phytomenadione (vitamin K1) and belongs to the pharmacotherapeutic group of antihaemorrhagics, vitamin K and other haemostatics (WHO ATC code: B02BA01). Phytomenadione MM paediatric is authorised for oral, intramuscular, and intravenous administration. *(1)*

Vitamin K is required for the post-translational γ-carboxylation of clotting factors II (pro-thrombin), VII, IX and X and clotting inhibitors protein C and protein S. Although the clotting inhibitors protein C and protein S are also carboxylated by vitamin K, the global pro-coagulatory effect predominates. Thus, under normal physiological conditions, the coagulation system is balanced in favour of anticoagulation. *(2)*

All neonates have reduced vitamin K levels at birth. Vitamin K is not transported across the placenta efficiently and is poorly excreted into breast milk, thus infants are born with low to undetectable concentrations of vitamin K *(3)*. The human infant is therefore exposed to a small but potentially life-threatening risk of vitamin K deficiency bleeding (VKDB). The major nutritional risk is to those infants who are exclusively breastfed. Formula-fed infants are protected from VKDB, because vitamin K content of milk formula is typically 50-fold higher than human milk, providing average daily intakes of approximately 50 µg of vitamin K *(4)*.

Lack of vitamin K leads to an increased tendency to haemorrhagic disease in the newborn. VKDB is a disorder of haemostasis that is caused by reduced activity of vitamin K-dependent coagulation factors, has normal or even increased activity of vitamin K-independent coagulation factors, and responds to vitamin K treatment. It presents as unexpected bleeding, often with gastrointestinal haemorrhage, ecchymosis and, in many cases, intracranial haemorrhage *(5)*. In newborns, it can be separated into three categories based on the timing of presentation. Early VKDB presents within 24 h after birth, classic VKDB in the first week, and late VKDB between one and twelve weeks of life *(6)*.

Early VKDB has been associated with mothers on anticonvulsants or other vitamin K interfering substances, and incidence without vitamin K supplementation has been reported as high as 12 %. Without vitamin K supplementation, the current day incidence of classic VKDB is estimated to be 0.25-1.7 %. The incidence of late VKDB in infants not given vitamin K prophylaxis has been demonstrated to be ~5 cases/100.000 births in Western European countries compared to 11 and 72/100.000 births in Japan and Thailand, with an increased risk in exclusively breastfed infants *(5)*. The relative risk for developing VKDB in unprotected breast-fed neonates compared with those given adequate parenteral vitamin K prophylaxis has been estimated to be 81:1 *(7)*. In contrast, VKDB is rare after intramuscular prophylaxis, with a reported incidence in epidemiological surveillance studies of ~1/100.000 births *(8, 9)*.

It can be assumed that only a few parents will reject a vitamin K prophylaxis for their newborn (e.g., 1.7 % in New Zealand, 1.2 % in Australia and 0.3 % in Canada), so that the number of vitamin K treated infants roughly corresponds to the birth rate *(10-12)*.

Bleeding complications represent a high risk for infants. The severity and outcome of the bleeding is essentially related to the location of the event. Especially patients with intracranial bleeding are exposed to a particularly high risk with a potentially fatal outcome. For example, late VKDB infants typically present with intracranial bleeding, which may result in permanent neurological damage or death. The mortality of late VKDB is 20-50 % *(2, 6)*.

Thus, vitamin K treatment can be lifesaving under certain circumstances and, therefore, the WHO already has classified the active ingredient phytomenadione as an essential medicine *(13)*. Although some other medicinal products containing phytomenadione are authorised worldwide, phytomenadione MM 2 mg/0.2 mL is one of the few and in some cases the only product in a country that can be administered intravenously or intramuscularly. This is extremely important, especially as it is often used in life-threatening situations, in which a rapid increase in plasma levels is required.

There are no alternative drugs to phytomenadione for the prevention and treatment of VKDB in newborns.

6.2 Phytomenadione MM 10 mg/1 mL

Phytomenadione MM 10 mg/1 mL is indicated for the treatment of haemorrhage or risk of haemorrhage as a result of severe 'hypoprothrombinaemia' (i.e. deficiency of clotting factors II, VII, IX and X) of various aetiologies, including overdosage of coumarin-type anticoagulants, their combination with phenylbutazone and other forms of hypovitaminoses K (e.g. in obstructive jaundice as well as liver and intestinal disorders, and after prolonged treatment with antibiotics, sulphonamides or salicylates). It contains the active ingredient phytomenadione (vitamin K1) and belongs to the pharmacotherapeutic group of antihaemorrhagics, vitamin K and other haemostatics (WHO ATC code: B02BA01). Phytomenadione MM is authorised for oral and intravenous administration. *(14)*

Vitamin K is required for the post-translational γ-carboxylation of clotting factors II (pro-thrombin), VII, IX and X and clotting inhibitors protein C and protein S. Although the clotting inhibitors protein C and protein S are also carboxylated by vitamin K, the global pro-coagulatory effect predominates. Thus, under normal physiological conditions, the coagulation system is balanced in favour of anticoagulation. *(2)*

Vitamin K is considered as a micronutrient due to its efficient recycling system in the organism *(3)*. It is supplied to the body in sufficient quantities via the food, if the diet is balanced. In normally healthy adults, 8-31 % have vitamin K deficiency. However, it is very rare to result in clinically significant bleeding. Cases are limited to individuals with malabsorption syndromes and those treated with drugs that interfere with vitamin K metabolism *(3)*.

Phytomenadione MM 10 mg/1 mL is indicated in the case of haemorrhage or risk of haemorrhage due to overdosed oral coumarin-type anticoagulants (vitamin K antagonists, VKA) represented by an increased INR (International Normalised Ratio of prothrombin time). VKAs (phenprocoumon, warfarin, acenocoumarol, fluindione) are widely prescribed for the prevention and treatment of thromboembolic complications. In 15 to 30 % of cases, vitamin K antagonist overdose is asymptomatic - an asymptomatic overdose is defined by an INR value outside of the therapeutic range without any clinical sign of haemorrhage. It is a risky situation that needs to be quickly managed to avoid bleeding

complications. Notably, in a US national surveillance project, warfarin was ranked among the drugs most commonly implicated in adverse events treated in emergency departments *(15)*. An INR range from 2 to 3 confers the lowest rate of a composite outcome of major bleeding and symptomatic thromboembolism and is thus the target for most indications *(16)*. Reversing the action of VKAs is needed in case of bleeding, surgery or interventions with a high bleeding risk, or VKA-coagulopathy as indicated by an INR above the therapeutic range. In patients with substantially elevated INRs (above 5), supplementation of vitamin K leads to a more rapid decline of the INR than just withholding VKAs *(15)*.

Approximately 15 to 20 per 1000 subjects in the Western world use VKAs, and this number is increasing, probably due to aging of the population and increasing adherence to guidelines *(16, 17)*. Phytomenadione supplementation to asymptomatic patients is unknown.

Even if the referenced information is already several years old and despite the introduction of direct oral anticoagulants (DOACs) as competitor products in some indications, VKA therapy is still broadly used for other indications or in economical situations where DOACs cannot be afforded *(18)*. Additionally, patients who are well adjusted to VKAs will probably remain on this form of therapy.

Bleeding complications represent a high risk. The severity and outcome of the bleeding is essentially related to the location of the event. Especially patients with intracranial bleeding are exposed to a particularly high risk with a potentially fatal outcome. For example, a study published by Steinberg et al. demonstrated, that 3.5 major bleeding events per 100 patient years among patients receiving the vitamin K antagonist warfarin occurred. Within 30 days, 7 % of these patients died *(19)*. In France, two national studies in 1998 and 2007 conducted by pharmacovigilance centres revealed that around 13 % of hospital admissions for adverse events are related to haemorrhage with VKAs, with about 17.000 hospitalisations and 5.000 deaths per year *(20)*.

Thus, vitamin K treatment can be lifesaving under certain circumstances and, therefore, the WHO has classified the active ingredient phytomenadione as an essential medicine *(21)*. Although some other medicinal products containing phytomenadione are authorised worldwide, phytomenadione MM 10 mg/1 mL is one of the few and in some cases the only product in a country that can be administered intravenously. This is extremely important, especially as it is often used in life-threatening situations, in which a rapid increase in plasma levels is required.

There are no alternative drugs to phytomenadione as antidot for VKA overdose.

7. Treatment details

7.1 Phytomenadione MM paediatric 2 mg/0.2 Ml *(1)*

Prophylaxis:

For all healthy neonates of 36 weeks gestation and older:

- 1 mg administered by intramuscular injection at birth or soon after birth or
- 2 mg orally at birth or soon after birth; the oral dose should be followed by a further dose of 2 mg at four to seven days of age. A further 2 mg oral dose should be given 1 month after birth. In exclusively formula-fed infants the third oral dose can be omitted.

A single 1 mg (0.1 mL) dose intramuscularly is recommended in children who are not assured of receiving a second oral dose or, in the case of breast-fed children, who are not assured of receiving a third oral dose.

Preterm neonates of less than 36 weeks gestation, weighing 2.5 kg or greater, and term neonates at special risk (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics):

- 1 mg intramuscularly or intravenously at birth or soon after birth. The amount and frequency of further doses should be based on coagulation status.

Preterm neonates of less than 36 weeks gestation, weighing less than 2.5 kg:

- 0.4 mg/kg (equivalent to 0.04 ml/kg) intramuscularly or intravenously at birth or soon after birth. This parenteral dose should not be exceeded. The amount and frequency of further doses should be based on coagulation status.

Therapy:

- Initially, 1 mg by intravenous injection, with further doses as required, based on the clinical picture and coagulation status.
- In certain circumstances, treatment with Konakion MM paediatric may need to be accompanied by more direct forms of effective haemorrhage control, such as transfusion of whole blood or coagulation factors, to compensate for severe blood loss and the delayed response to vitamin K1.

Requirements to ensure appropriate use of the medicine:

- The ampoule solution should not be mixed with other parenteral medications medications, but may be injected, where appropriate, into the lower part of the infusion set.
- Adjusted volumes of 1:5 or 1:10 dilutions in glucose 5% can be administered.
- For oral use, the included adapter or a syringe can be used.
- At the time of use, the mixed-micelle ampoule solution must be clear in appearance.
- The glass ampoules must be kept in the outer carton in order to protect from light.

7.2 Phytomenadione MM 10 mg/1 mL *(14)*

Standard dosage:

Severe or life-threatening haemorrhage, e.g. during anticoagulant therapy: The coumarin anticoagulant should be withdrawn and an i.v. injection of Konakion MM given slowly (in at least 30 seconds) in a dose of 5-10 mg together with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). The dose of Vitamin K1 can be repeated as needed.

Dose recommendations for vitamin K1 therapy in patients with asymptomatic high International Normalized Ratio (INR) with or without mild haemorrhage:

Anticoagulant	INR	Oral vitamin K_1	Intravenous vitamin K_1
Warfarin	5-9	1.0 to 2.5 mg for initial reversal 2.0 to 5.0 mg for rapid reversal (add. 1.0 to 2.0 mg if INR remains high after 24 h)	0.5 to 1.0 mg 0.5 to 1.0 mg
	>9	2.5 to 5.0 mg (up to 10.0 mg)	1.0 mg
Acenocoumarol	5-8	1.0 to 2.0 mg	1.0 to 2.0 mg
	>8	3.0 to 5.0 mg	1.0 to 2.0 mg
Phenprocoumon	5-9	2.0 to 5.0 mg	2.0 to 5.0 mg
	>9	2.0 to 5.0 mg	2.0 to 5.0 mg
	>10	Not recommended	Individually adapted doses

Dose recommendations for vitamin K1 therapy in patients with major and life-threatening bleeding:

Anticoagulant	Condition	Intravenous vitamin K_1	Concomitant therapy
Warfarin	**Major bleeding**	5.0 to 10.0 mg	FFP or PCC
	Life-threatening bleeding	10.0 mg	FFP, PCC, or recombinant factor VIIa
Acenocoumarol	**Major bleeding**	5.0 mg	FFP, PCC, or prothrombin concentrates and factor VII
Phenprocoumon	**Major bleeding with INR <5.0**	5.0 mg	PCC
	Major bleeding with INR >5.0	10.0 mg	PCC

FFP, fresh frozen plasma
PCC, prothrombin complex concentrate

For small doses one or more ampoules of Konakion MM paediatric (2 mg/0.2 mL; same solution) can be used.

Use in the elderly:

- Elderly patients tend to be more sensitive to reversal of anticoagulation with Konakion.
- The dosage for this patient group should therefore be at the lower end of the ranges recommended.
- Small doses of 0.5 to 1.0 mg i.v. or oral vitamin K1 have shown to effectively reduce the INR to <5.0 within 24 hours.

Children over one year of age:

- The optimal dose should be decided by the treating physician according to the indication and weight of the patient.
- A single dose of one tenth of the full i.v. adult dose of vitamin K1 has been reported to be effective in reversing asymptomatic high (>8) INR in clinically well children.

Infants under one year of age:

- For this patient group, Konakion MM paediatric should be used.

Requirements to ensure appropriate use of the medicine:

- For small doses one or more ampoules of Konakion MM paediatric (2 mg/0.2 mL; same solution) can be used.
- The ampoule solution should not be mixed with other parenteral medications, but may be injected, where appropriate, into the lower part of the infusion set.

- For oral use, a syringe (not provided) can be used.
- At the time of use, the mixed-micelle ampoule solution must be clear. Following incorrect storage, the solution may become turbid or a phase separation may occur. In such cases, the ampoule must not be used.
- Careful monitoring of the INR is necessary after administration of Konakion MM in patients with severely impaired liver function.
- The glass ampoules must be kept in the outer carton in order to protect from light.

8. Review of evidence for benefits and harms

Konakion with its active ingredient phytomenadione had been developed by F. Hoffmann-LA Roche Ltd and obtained first market authorisation on 1 January 1954 in Angola. The product initially contained phytomenadione in the solvent Cremophor EL and was then further developed into the mixed micelle system (Konakion MM, phytomenadione MM).

CHEPLPHARM took over the product from Roche in 2018 at a time when the Cremophor-based formulation had not been marketed for years and only the phytomenadione MM had been produced. Therefore, most of the clinical comparative studies are available for these two formulations and are mostly original study reports from Roche, which have only been partially published for the public. In these, the old formulation is referred to as Konakion, Konakion drops or Konakion N, while the new formulation is called Konakion MM. For better comprehensibility, the brand names are mentioned in the quotations of the original studies, while the Konakion MM is generally referred to as phytomenadione MM.

In addition, a systematic literature search was carried out to identify trials and systematic reviews, comparing at least one different phytomenadione formulation to phytomenadione MM. Searches in the company own literature data base and PubMed were conducted using the keywords “Konakion MM” “phytomenadione MM”, “Konakion mixed micelle” and “phytomenadione mixed micelle”. The search results in PubMed were then narrowed down to the types: meta-analysis, randomised controlled trials, reviews and systematic reviews.

Two blood parameters are often analysed to assess vitamin K deficiency and the effectiveness of treatment with phytomenadione formulations: vitamin K1 itself and PIVKA-II (Protein induced by vitamin K absence-II). PIVKA-II can detect undercarboxylated species of factor II well before there are any changes in global coagulation assays such as the prothrombin time. Whereas detectable concentrations of PIVKA-II are rarely detected in healthy adults, elevated concentrations are fairly common in the cord blood of healthy newborns suffering from vitamin K deficiency *(4)*.

8.1 Phytomenadione MM paediatric 2 mg/0.2 mL

Efficacy – published reports

There are four reports in the literature comparing the efficacy of Konakion (Cremophor EL) to Konakion MM in children:

Greer et al.: A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants *(22)*

- 1 mg intramuscular injection of vitamin K1 (Konakion, Cremophor EL, n=77) or a 2 mg oral dose of the experimental preparation (Konakion MM, n=79, time points: after birth, 7 and 30 days)
- The concentrations were highest on day 14 in both groups, although the concentrations in the oral group were significantly higher than the IM group.
- By day 30, there was no significant difference between the two groups.
- At 56 days, the concentrations in the oral group were significantly higher than the IM group.
- At the time of birth 47% of all infants had positive PIVKA-II values.
- There were only two positive PIVKA-II values at 14 days (one in each group), none at 28 days, and three at 56 days (all in the IM group).
- At 56 days, the three raised PIVKA-II values were associated with low vitamin K1.
- There were no major adverse events attributed to the vitamin K preparations used in this study, at least during the first 2 months of life.
- There were no bleeding episodes of any kind.
- Through the first 8 weeks of life, multiple doses of the new oral preparation maintain haemostasis and vitamin K status in breast fed infants at least equal to that of the intramuscular preparation.

Schubiger et al.: Plasma vitamin K1 and PIVKA-II after oral administration of mixed-micellar or cremophor EL-solubilized preparations of vitamin K1 to normal breast-fed newborns *(23)*

- Single oral 2 mg Konakion MM (n=14) versus oral 2 mg Konakion Cremophor EL (n=16)
- Plasma samples were taken at 24 hours, 4 days, and 24 days after birth.
- The concentrations of vitamin K1, PIVKA-II, and total bound bilirubin were measured.
- The median concentration of plasma vitamin K1 was higher at all three time points in the group that received the mixed-micellar preparation, but the difference was only significant ($p < 0.05$) at 4 days.
- At 24 hours and 4 days, PIVKA-II was detectable in a significantly lower proportions of infants receiving the new mixed-micellar preparation than those receiving the Cremophor EL preparation.
- None of the infants in the study had detectable PIVKA-II levels 24 days after birth.
- Results suggest that when given orally, the mixed-micellar preparation is superior to the conventional formulation because it increases plasma vitamin K1 concentrations to higher levels, suggesting superior bioavailability, and decreases PIVKA-II concentrations more efficiently, suggesting a faster pharmacodynamic response.

Amédée-Manesme et al.: Pharmacokinetics and safety of a new solution of vitamin K1(20) in children with cholestasis *(24)*

- Part 1: 40 infants with chronic cholestasis, single i.m. 1 mg Konakion Cremophor EL (n=20) versus i.m. 1 mg Konakion MM (n=20) → no adverse events and no significant differences in blood parameters
- Part 2: 9 infants with biliary atresia, single oral 20 mg Konakion Cremophor EL (n=3) versus oral 20 mg Konakion MM (n=3) versus i.m. 10 mg Konakion MM (n=3)
    - → low serum peak values after oral Konakion (Cremophor EL) but very high levels after oral Konakion MM
    - → Konakion MM i.m. resulted in high vitamin K levels comparable to the levels obtained with the double-dose oral Konakion MM
    - → no adverse events

- Part 3: 22 infants and children, i.m. 10 mg Konakion Cremophor EL biweekly for 6 month, followed by oral 10 mg Konakion MM or 10 mg i.m. Konakion MM, both over 3 month → highest vitamin K levels in i.m. group, mean vitamin K level after oral administration was still high
- Results demonstrate superiority of the MM formulation.
- After oral administration, even patients suffering from fat malabsorption, enhanced absorption was observed to Konakion MM administration.

von Kries et al: Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding *(25)*

- 1 817 769 newborns exposed orally to the mixed micellar preparation and 1 320 926 newborns exposed orally to other preparations.
- Confirmed VKDB between day 8 and week 12: 17 VKDB (7 with MM, 9 with others, 1 with both)
- The rate of late VKDB was 0.44/100 000 (95% confidence interval (CI) 0.19 to 0.87) in children given mixed micellar vitamin K compared with 0.76/100 000 (95% CI 0.36 to 1.39) in children given other preparations. → Mixed micellar vitamin K did not significantly improve the efficacy of the 3 × 2 mg oral vitamin K prophylaxis schedule.

It should be noted, that VKDB after complete phytomenadione prophylaxes (3x2 mg orally) is extremely low *(7)* and mainly affects children suffering from cholestasis, who would need higher doses for protection, however, in most cases, the disease is not yet known at the time of treatment *(24, 26)*. These circumstances make it extremely difficult to conduct meaningful comparative studies, since an almost impossibly high number of patients would have to be treated. It is therefore not surprising that differences found were not significant between different formulations (although the lower numbers of VKDB for Konakion MM suggest that there might be a better protection), nor that there are a large number of such studies.

Efficacy – unpublished data

In nine clinical studies conducted by F. Hoffmann-LA Roche Ltd, a total of 182 infants were treated with oral, intramuscular or intravenous phytomenadione MM, partly in comparison with phytomenadione (Cremophor EL).

Roche Report B-115-018: Tolerability of Ro 01-6722/120 in infants with stable cholestasis *(27)*

- 10 infants, single i.m. 5 mg Konakion MM (Ro 01-6722/120) in an open pilot study
- All babies showed the clinical picture of a stable icterus. Their diagnoses were: biliary duct atresia, neonatal cholestasis, rare bilary ducts and tyrosinemia.
- Glycocholic acid as an essential part of the mixed micelles is strongly bound to serum albumin in blood like bilirubin. → The possibility of a displacement of bilirubin from the protein binding by glycocholic acid and the resulting danger of kernicterus has to be clarified.
- Before treatment and 3-6 days after the injection, the coagulation factors 1, 2, 5, 7 + 10, quick and the cephaline-kaolin time as well as total and conjugated bilirubin, SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamate pyruvate transaminase), gamma-GT (gamma-glutamyl transferase), alkaline phosphatase and biliary acids were determined. Three to six days later the same parameters as above were determined.
- No increase neither of total nor of conjugated bilirubin; no significant modification of trans-aminases, gamma-GT, alkaline phosphatases and biliary acids was observed.
- Konakion MM was able to correct any abnormality in haemostasis present in some of the infants.

- No side-effects and especially no allergic reactions were observed.

Roche Report B-117-130: Pharmacokinetics of a single dose of vitamin (10 mg) mixed micelles solution administered intramuscularly to 4 cholestatic babies *(28)*

- 4 cholestatic babies, single i.m. 10 mg Konakion MM
- Blood samples were taken at 0, 3, 6, 9, 12, 18, 24, 30, 36, 48, 60, 72 and 96 h for:
    - The evaluation of total and bound bilirubin and of the percentage of bilirubin binding
    - The assessment of the profile of the plasma levels of vitamin K1
    - The evaluation of blood clotting at 0 h and at 96 h.
- The i.m. injection of vitamin K1 (10 mg) mixed micelles solution rapidly established a high concentration in the plasma of the patients, peaking at 12 hours at 2174 ng/ml. This indicates an excellent bioavailability of the vitamin K1 mixed micelles solution injected intramuscularly.
- By 96 hours after the injection the plasma concentration drops to 14 ng/ml, which indicates a good utilisation.
- No changes in the concentrations of bound bilirubin expressed as percentage of total bilirubin were observed.
- It was very well tolerated.
- The data of this trial suggest that the Konakion MM given orally within 4 hours after birth is a safe, effective and convenient product for routine prophylaxis of haemorrhagic disease of the newborn.

Roche Report B-115-046: Bioavailability and efficacy of KONAKION MM Ro 01-6722/130, 1.5 mg vitamin K1 i.m. versus 3.0 mg vitamin K1 oral in healthy new-born breast-fed babies *(29)*

- 25 babies, single i.m. 1.5 mg Konakion MM (n=10) versus oral 3 mg Konakion MM (n=15)
- Blood samples were taken immediately after birth, after 24 hours and 24 days after treatment and plasma levels of vitamin K1 were determined.
- The difference of vitamin K1 plasma levels between the two types of treatment is statistically significant after 24 hours (higher levels after oral administration), but no more after 24 days.
- With the oral administration of 3 mg vitamin K1 the Quick value can be raised over the minimal normal adult value of 70 % within 24 hours after administration. On the other side the i.m. treatment with 1.5 mg vitamin K1 after birth did not raise the Quick value at 24 hours at all.
- The oral treatment protects newborns much better from haemorrhagic disease during the critical period in the early days of live.
- All laboratory parameters (SGOT, SGPT and alkaline phosphatase) are in the normal range 24 hours and 24 days after administration.
- Treatment is without side effects.
- The data of this trial suggest that the Konakion MM given orally within 4 hours after birth is a safe, effective and convenient product for routine prophylaxis of haemorrhagic disease of the newborn.

Roche Report B-115-048: Bioavailability of KONAKION MM, Ro 01-6722/130, oral and parenteral in mature neonates at birth (> 2000 g) and the evolution of vitamin K1 plasma level in breast-fed babies *(30)*

- 25 babies, single oral 3 mg Konakion MM (n=14) versus i.m. 1.5 mg Konakion MM (n=11)
- A first blood sample was taken 24 hours, a second sample 4 days and a third sample 24 days after administration.

- 24 h after treatment vitamin K1 levels reached 154 ng/ml after i.m. and 105.38 ng/ml after oral administration.
- After 24 days only 1 % of vitamin K1 was found when administered i.m. and 0.5 % when administered orally in relation to the original peak values at 24 hours.
- No bilirubin displacement from albumin could be found.
- No adverse events were reported.
- It can be concluded that Konakion MM is a safe and effective drug for routine treatment to protect newborns from haemorrhagic disease.

Roche Report B 159-050: Pharmacokinetics and safety of a new solution of vitamin K1(20) in children with cholestasis *(26)*

- 13 cholestatic infants, single oral 20 mg Konakion MM (n=6) versus i.m. 10 mg Konakion MM (n=7)
- There is virtually no absorption of vitamin K1 in these patients due to lack of bile-acids.
- Vitamin K1 level in plasma was measured before and 3, 6, 12, 24, 48 hours and 4 days after administration.
- With double the amount of Konakion (20 mg K1) orally administered, the same plasma levels were achieved as with 10 mg vitamin K1 i.m..
- For the oral dose (20 mg K1) and the i.m. dose (10 mg K1) the plasma levels of vitamin K1 was raised sharply to reach peak concentration at 3 hours after administration.
- The vitamin K1 levels decreased to levels comparable to those measured before administration of Konakion MM within 72 hours for both ways of administration.
- The hypothesis that under the circumstances of cholestasis the oral administration of Konakion MM solution would promote the absorption of vitamin K1 could be confirmed. No adverse events have been reported by the investigators.

Roche Report B-159-051: Efficacy and tolerability of KONAKION MM 2 mg vitamin K1 orally versus 1 mg vitamin K1 intramuscularly in new-born, breast-fed babies *(31)*

- 13 babies, single i.m. 1 mg Konakion MM (n=7) versus oral 2 mg Konakion MM (n=6)
- The first blood sample was taken before treatment (0 hour). The 2nd sample was taken 3 hours after treatment followed by sampled taken after 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours.
- The efficacy parameters analysed were vitamin K1 levels in plasma 24 hours after application, the clotting factors and prothrombin time at 24 hours and 24 days after administration of the vitamin.
- The two application routes and dosages gave equal plasma levels.
- No bilirubin displacement from albumin could be found.
- Prothrombin had significantly increased during the first 24 days in both routes of administration.
- No adverse events were reported.
- The product is safe and effective for the routine treatment of newborns.

Roche Report B 162-000: Randomised comparative trial to evaluate efficacy and tolerability of KONAKION MM, Ro 01-6722/135, KONAKION drops Ro 01-6722/070, orally and KONAKION ampoules Ro 01-6722/119 intramuscularly in the prophylaxis of haemorrhagic disease in new-born, breast-fed infants *(32)*

- 148 newborns, single oral 2 mg Konakion MM (n=50) versus oral 2 mg Konakion drops (Cremophor EL, n=48) versus i.m. 1 mg Konakion Cremophor EL (n=50)
- 4 weeks after dosing the plasma concentrations of vitamin K were significantly higher in the group that had received Konakion MM compared to the other two groups.
- It can be concluded that in infants receiving Konakion MM 2 mg p.o. after birth the average plasma level after 4 weeks is still above the average physiological level of 0.5 ng/ml, whereas at the same time the average plasma level for the Konakion drops 2 mg or Konakion 1 mg i.m. is below the average physiological level.
- At 4 weeks the difference of the means of Thrombotest values between Konakion MM 2 mg p.o. and Konakion drops 2 mg p.o. is statistically highly significant, whereas the difference between Konakion MM 2 mg p.o. and Konakion 1 mg i.m. and the difference between Konakion drops and Konakion 1 mg i.m. are both statistically not significant.
- After 4 weeks all the PIVKA-II values were below 0.13 AU/ml.
- There were no adverse events reported for all three products.
- Konakion MM has superior efficacy measured by plasma levels of vitamin K, PIVKA-II and Thrombotest compared to the old oral product.
- The new physiological solubilising system makes enough vitamin K1 available to the liver in order to carboxylate all vitamin-K-dependent proteins in order to protect all and especially breast-fed infants from all types of haemorrhagic disease.

Roche Report B-162-001: Plasma vitamin K1 and PIVKA-II after oral administration of mixed-micellar or cremophor EL-solubilised preparations of vitamin K1 to normal breast-fed newborns *(33)*

- 30 newborns, single oral 2 mg Konakion MM (n=14) versus oral 2 mg Konakion Cremophor EL (n=16)
- Plasma samples were taken at 24 hours, 4 days, and 24 days after birth.
- The concentrations of vitamin K1 (24 h, 4 days, 24 days) and PIVKA-II (24 h, 4 days) were measured.
- At 4 days and 24 days the vitamin K1 plasma levels are statistically significant lower after administration of Konakion Cremophor EL than after administration of Konakion MM.
- For Konakion (Cremophore EL) a more rapid decrease (68 %) of these levels was observed than for Konakion MM.
- In the groups which had received Konakion Cremophor EL highly significant more positive PIVKA-II values were observed than after administration of Konakion MM after 24 hours and 4 days.
- The efficient elimination of PIVKA's with Konakion MM indicates that as a result of more efficient absorption and distribution of vitamin K due to a physiological solubilising system enough vitamin K is available to carboxylate all vitamin-K-dependent proteins and to protect infants from all types of haemorrhagic disease.

This study was also published for the public *(23)*.

Roche Report B-162-002: Efficacy and tolerability of KONAKION MM Ro 01-6722/135 1 mg vitamin K1 i.v. and 2 mg vitamin K1 p.o. in the prophylactic treatment against haemorrhagic disease in premature infants *(34)*

- 28 premature infants, single i.v. 1 mg Konakion MM followed by oral 2 mg Konakion MM every 4 weeks until the end of the intensive care period
- A plasma sample was taken at day 4 and after four weeks and plasma vitamin K1 levels and PIVKA-II were determined.
- The average vitamin K1 plasma level after 4 days was not different from those found in previous clinical studies with healthy newborns.
- At 4 weeks the average plasma level was still above the upper limit of the physiological adult level of 0.7 ng/ml.
- 55 % of the premature infants had positive PIVKA-II in the cord-blood. At day 4, 20 % had still positive PIVKA-II and at 4 weeks all positive PIVKA-II were eliminated.
- No adverse events were reported.
- I.v. administration of Konakion MM is an effective and well tolerated prophylaxis of haemorrhagic disease also in premature infants.

In summary, the study authors concluded that vitamin K from phytomenadione MM given orally to newborns is absorbed and distributed in the body very efficiently to protect from haemorrhagic disease. Additionally, phytomenadione MM is superior to the conventional formulation through faster absorption and represents an effective treatment of vitamin K1 deficiency, especially when there is a lack of bile-salt as it is the case in cholestatic infants, low-birth-weight premature and some normal full-term neonates.

Safety – published data

There is one report in the literature comparing the safety of Konakion (Cremophor EL) to Konakion MM in children and adults and one report comparing the oral and intramuscular route of Konakion MM in the newborn.

Pereira and Williams: Adverse events associated with vitamin K1: results of a worldwide postmarketing surveillance programme *(35)*

- 635 million adults and 728 million children were prescribed Konakion (Cremophor EL) or Konakion MM.
- Eighty-five probable anaphylactoid reactions (of which six were fatal) were reported for conventional Konakion (Cremophor EL).
- One non-fatal anaphylactoid reaction was reported for Konakion MM.
- Last 12 months of postmarketing surveillance: 14 serious adverse events reported in an estimated 21 million individuals treated with Konakion (Cremophor EL), but none in the 13 million who received Konakion MM.
- These results suggest Cremophor EL-solubilised preparations of vitamin K1 have a higher profile of adverse events, including anaphylactoid reactions, than the newer mixed micellar preparation, Konakion MM.

Schubiger et al.: Vitamin K1 concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone *(36)*

- 25 babies, single i.m. 1.5 mg Konakion MM (n=11) or oral 3 mg Konakion MM (n=14) after birth
- Venous blood samples were collected at 25 h, 4 days, and 24 days.
- After p.o. administration, the median plasma vitamin K concentration increased to 89 ng/ml after 24 h, then decreased to 51 ng/ml after 4 days; the respective concentrations after i.m. injection were 146 ng/ml and 34 ng/ml.
- The higher plasma vitamin K level in the i.m. group after 24 h was not statistically significant compared with that of the p.o. group, but the reversed higher concentration in the p.o. group after 4 days was significant ($p < 0.01$).
- After 24 days the median plasma vitamin K had decreased to 0.44 ng/ml (range 0.19-1.44) and 1.05 ng/ml (range 0.37-1.87) in the p.o. and i.m. groups, respectively.
- The narrow range of plasma concentrations at 24 h and 4 days suggests a greater consistency of absorption from this micellar preparation than from other emulsion-based preparations.

Safety – unpublished data

In 11 clinical trials performed by F. Hoffmann-LA Roche Ltd, overall, 213 infants were treated with phytomenadione MM through the intramuscular, intravenous and oral route. Some of these studies involved the administration of phytomenadione MM alone, while others were comparative studies with Cremophor EL-phytomenadione. All studies were free from adverse reactions.

Roche Report B-115-018: Tolerability of Ro 01-6722/120 in infants with stable cholestasis *(27)*

- For efficacy data please refer to paragraph “Efficacy – unpublished data”
- 10 infants, single i.m. 5 mg Konakion MM (Ro 01-6722/120) in an open pilot study
- No increase neither of total nor of conjugated bilirubin; no significant modification of trans-aminases, gamma-GT, alkaline phosphatases and biliary acids was observed.
- No side-effects and especially no allergic reactions were observed.

Roche Report B-117-130: Pharmacokinetics of a single dose of vitamin (10 mg) mixed micelles solution administered intramuscularly to 4 cholestatic babies *(28)*

- For efficacy data please refer to paragraph “Efficacy – unpublished data”
- 4 cholestatic babies, single i.m. 10 mg Konakion MM
- No changes in the concentrations of bound bilirubin expressed as percentage of total bilirubin were observed.
- It was very well tolerated.

Roche B-117-131: Comparative tolerability and efficacy study: vitamin mixed micelles solution versus vitamin solution containing Cremophor EL both administered in a single dose i.m., to babies suffering from chronic cholestasis *(37)*

- 40 babies, single i.m. 10 mg Konakion MM (n=20) or Konakion Cremophor EL (n=20) after birth
- Local and the general tolerability of the new formulation of vitamin K1 were excellent (also excellent in Cremophor group).
- No significant changes in the hepatic transaminase, gamma-glutamyl transferase, or alkaline phosphatase values were observed.
- Bile acid levels remained unchanged.

- Both formulations did not lead to an increase in either the total or the bound bilirubin levels.

Roche Report B-115-040: Comparative tolerability of Ro 01-6722/120 (KONAKION MM) and Ro 01-6722/092 (KONAKION commercial form with Cremophor 5 mg/0.5 ml i.m. in healthy new-born and premature babies *(38)*

- 17 babies, single i.m. 5 mg Konakion MM (n=10) or Konakion Cremophor EL (n=7) after birth
- Laboratory values showed no statistically significant differences between the two products (haemoglobin, erythrocytes, thrombocytes, bilirubin total, alkaline phosphatase, biliary salts).
- Neither allergic reactions nor irritations at the injection site were observed for both products.
- It can therefore be assumed that Konakion MM is safe in new-born and premature babies.

Roche Report B-115-046: Bioavailability and efficacy of KONAKION MM Ro 01-6722/130, 1.5 mg vitamin K1 i.m. versus 3.0 mg vitamin K1 oral in healthy new-born breast-fed babies *(29)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 25 babies, single i.m. 1.5 mg Konakion MM (n=10) versus oral 3 mg Konakion MM (n=15)
- All laboratory parameters (SGOT, SGPT and alkaline phosphatase) are in the normal range 24 hours and 24 days after administration.
- Treatment is without side effects.
- The data of this trial suggest that the Konakion MM given orally within 4 hours after birth is a safe, effective and convenient product for routine prophylaxis of haemorrhagic disease of the newborn.

Roche Report B-115-048: Bioavailability of KONAKION MM, Ro 01-6722/130, oral and parenteral in mature neonates at birth (> 2000 g) and the evolution of vitamin K1 plasma level in breast-fed babies *(30)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 25 babies, single oral 3 mg Konakion MM (n=14) versus i.m. 1.5 mg Konakion MM (n=11)
- No bilirubin displacement from albumin could be found.
- No adverse events were reported.
- It can be concluded that Konakion MM is a safe and effective drug for routine treatment to protect newborns from haemorrhagic disease.

Roche Report B-159-050: Comparative bioavailability and kinetics of KONAKION MM; Ro 01-6722/120, oral and parenteral in infants suffering from chronic cholestasis *(26)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 13 patients, single oral 20 mg Konakion MM (n=6) versus i.m. 10 mg Konakion MM (n=7)
- No adverse events have been reported.

Roche Report B-159-051: Efficacy and tolerability of KONAKION MM 2 mg vitamin K1 orally versus 1 mg vitamin K1 intramuscularly in new-born, breast-fed babies *(31)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 13 babies, single i.m. 1 mg Konakion MM (n=7) versus oral 2 mg Konakion MM (n=6)
- No bilirubin displacement from albumin could be found.
- No adverse events were reported.
- The product is safe and effective for the routine treatment of newborns.

Roche Report B-162-000: Randomised comparative trial to evaluate efficacy and tolerability of KONAKION MM, Ro 01-6722/135, KONAKION drops Ro 01-6722/070 orally and KONAKION ampoules Ro 01-6722/119 intramuscularly in the prophylaxis of haemorrhagic disease in new-born, breast-fed infants *(32)*

- 148 babies, single oral 2 mg Konakion MM (n=50) versus oral 2 mg Konakion drops (Cremophor EL, n=48) versus i.m. 1 mg Konakion ampoules (Cremophor EL, n=50)
- No adverse events were reported for all three products.

Roche Report B-162-001: Bioavailability and efficacy of KONAKION MM ampoules vs KONAKION drops in healthy new-born at term (>2000 g) breast-fed infants 2 mg per os *(33)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 30 babies, single oral 2 mg Konakion MM (n=15) versus oral 2 mg Konakion drops (n=15)
- No adverse events were recorded.

Roche Report B-162-002: Efficacy and tolerability of KONAKION MM Ro 01-6722/135 1 mg vitamin K1 i.v. and 2 mg vitamin K1 p.o. in the prophylactic treatment against haemorrhagic disease in premature infants *(34)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 28 premature infants, single i.v. 1 mg Konakion MM followed by oral 2 mg Konakion MM every 4 weeks until the end of the intensive care period
- No adverse events were reported.
- I.v. administration of Konakion MM is an effective and well tolerated prophylaxis of haemorrhagic disease also in premature infants.

In conclusion, a huge comparative safety study demonstrated a much better safety profile of phytomenadione MM compared to the Cremophor EL-containing formulation, as 97 % of anaphylactoid reactions in adults and children were associated with Cremophor EL-phytomenadione. Additionally, it was shown that phytomenadione MM was well tolerated by premature babies and newborns.

8.2 Phytomenadione MM 10 mg/1 mL

Efficacy – published data

There is one report in the literature comparing the efficacy and safety of Konakion (Cremophor EL) to Konakion MM in adults:

Soedirman et al.: Pharmacokinetics and tolerance of intravenous and intramuscular phylloquinone (vitamin K1) mixed micelles formulation *(39)*

- 30 adult volunteers, 10 mg Konakion MM i.v. and i.m. in an open randomised cross-over design protocol
- Blood samples were collected for up to 12 h after the intravenous and up to 72 h after the intramuscular injections.
- Konakion MM was well tolerated after either route of administration.

- Pharmacokinetic analysis of plasma vitamin K1 concentration vs time profiles revealed that in one-fifth of the subjects systemic availability of intramuscular vitamin K1 was below 65%.
- Data suggest that due to sustained, but irregular and unpredictable absorption of the vitamin K1 from the depot site, the intramuscular route of Konakion MM administration is not suitable and thus not recommended for anticoagulant reversal.
- Konakion MM i.v. is well tolerated and effective in antagonising coumarin-type-anticoagulants.

Efficacy – unpublished data

In two clinical trials performed by F. Hoffmann-LA Roche Ltd, overall, 50 healthy volunteers were treated with phytomenadione MM compared to phytomenadione (Cremophor EL) through the oral and intramuscular route.

Roche Report B 159-012: Bioavailability of three vitamin K1 preparations (Ro 01-6722 Konakion), cremophor /119, mixed micelles/131, and /141 relative to Tween 80/143 formulation (M10400/BK14677) *(40)*

- 20 healthy male subjects (19-47 years), four-way cross over study
- Blood samples were collected before treatment and after 10, 20, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 16 and 26 hours after administration.
- Treatment A: i.m. administration of 10 mg Tween 80 vitamin K1, Ro 01-6722/143
- Treatment B: i.m. administration of 10 mg Cremophor EL vitamin K1, Ro 01-6722/119
- Treatment C: i.m. administration of 10 mg Mixed Micelles vitamin K1, Ro 01-6722/131
- Treatment D: p.o. administration of 20 mg Mixed Micelles vitamin K1, Ro 01-6722/141
  → A and B: the pharmacokinetic profiles appear to be different, the systemic exposure (up to 26 h post administration) is 4.5 times greater with formulation B than with formulation A
  → A and C: exhibit similar flat pharmacokinetic profiles which are characteristic of i.m. depot preparations
  → D: following oral administration of the formulation D (Mixed Micelles), a marked peak of concentration in plasma was observed, showing that vitamin K1 was well absorbed after administration of the mixed micelles formulation

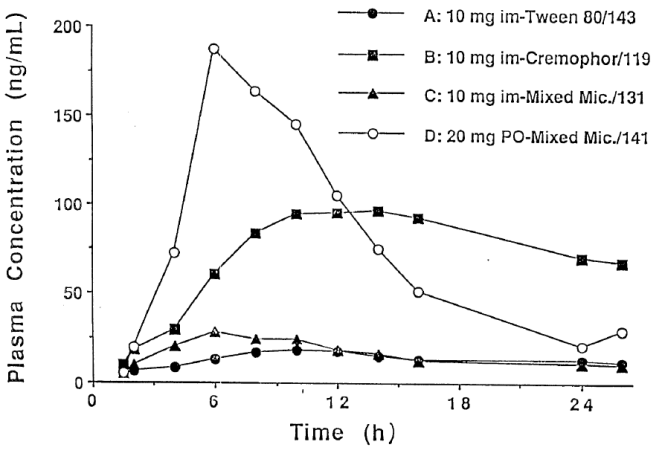

Figure 1: Mean plasma concentrations of vitamin K1 versus time after administration of 4 different formulations

- The pharmacokinetic profiles were characterised by a high variability. The lowest coefficient of variance was obtained after administration of the oral mixed micelle formulation D.
- All formulations were well tolerated.

Roche Report M 33230: Comparison of the bioavailabilities of Konakion MM 10 mg (Ro 01-6722/131) and Konakion N solution (Ro 01-6722/076) after oral administration of 10 mg of each *(41)*

- 30 healthy volunteers of both sexes, cross over study
- Single oral 10 mg Konakion (Cremophor EL) versus Konakion MM
- Blood samples were collected before treatment and after 10, 20, 30, 45 minutes and 1, 10, 12, 16, 24, 36, 48 and 72 hours after administration.

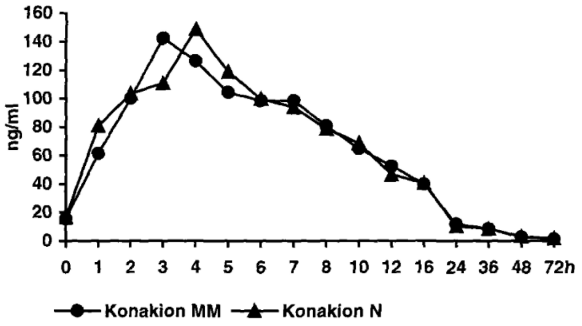

Figure 2: Mean plasma values of the serum vitamin K1 concentrations

- Both formulations are bioequivalent.

Safety – published data

There is one report in the literature comparing the safety of Cremophor EL-phytomenadione to phytomenadione MM in children and adults showing that 97 % of anaphylactoid reactions were associated with Cremophor EL-phytomenadione:

Pereira and Williams: Adverse events associated with vitamin K1: results of a worldwide postmarketing surveillance programme *(35)*

- 635 million adults and 728 million children were prescribed conventional Konakion (Cremophor EL) or Konakion MM
- Eighty-five probable anaphylactoid reactions (of which six were fatal) were reported for conventional Konakion.
- One non-fatal anaphylactoid reaction was reported for Konakion MM.
- Last 12 months of postmarketing surveillance: 14 serious adverse events reported in an estimated 21 million individuals treated with conventional Konakion, but none in the 13 million who received Konakion MM
- These results suggest Cremophor EL-solubilised preparations of vitamin K1 have a higher profile of adverse events, including anaphylactoid reactions, than the newer mixed micellar preparation, Konakion MM.

Safety – unpublished data

In two clinical studies performed by F. Hoffmann-LA Roche Ltd, 50 healthy volunteers were treated with phytomenadione (Cremophor EL) and phytomenadione MM through the intravenous and oral route. One study was free from serious adverse reactions *(40)* and in the other study no adverse event occurred *(41)*, demonstrating an overall good tolerability.

Roche Report B 159-012: Bioavailability of three vitamin K1 preparations (Ro 01-6722 Konakion), cremophor /119, mixed micelles/131, and /141 relative to Tween 80/143 formulation (M10400/BK14677) *(40)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 20 healthy male subjects (19-47 years), four-way cross over study
- 25 adverse events occurred in 13 subjects during the study.
- No serious adverse event was reported.
- In conclusion, all formulations were well tolerated.

Roche Report M 33230: Comparison of the bioavailabilities of Konakion MM 10 mg (Ro 01-6722/131) and Konakion N solution (Ro 01-6722/076) after oral administration of 10 mg of each *(41)*

- For efficacy data please refer to paragraph "Efficacy – unpublished data"
- 30 healthy volunteers of both sexes, cross over study
- Single oral 10 mg Konakion N versus oral 10 mg Konakion MM
- No adverse events occurred in the course of the study.

In conclusion, a huge comparative safety study demonstrated a much better safety profile of phytomenadione MM compared to the Cremophor EL-containing formulation, as 97 % of anaphylactoid reactions in adults and children were associated with Cremophor EL-phytomenadione. Additionally, it was shown that phytomenadione MM was well tolerated by healthy volunteers and patients. Overall, it was shown in both newborns and adults that phytomenadione as mixed micelle solution is usually absorbed faster or at least comparably after oral administration, which is a prerequisite for outstanding efficacy. In addition, the drug was shown to be exceptionally safe and well tolerated.

8.3 Phytomenadione MM solution for injection and oral administration versus phytomenadione tablets

According to WHO EML and WHO EMLc, phytomenadione-containing tablets are classified as essential medicine. Phytomenadione-containing tablets are authorised in the European Union (in Denmark) as 10 mg tablets, or in the USA as divisible 5 mg tablets and are indicated for the reversal of vitamin K antagonist overdoses. *(42, 43)*.

In the case of anticoagulation using vitamin K antagonists monitoring the anticoagulant effect by assessing the patient's international normalized ratio (INR) is essential because complications are closely related to the intensity of anticoagulation. Treatment with vitamin K antagonists contains a substantial risk of bleeding with a high case fatality rate. Reversal of vitamin K antagonists is required in case of bleeding or a supratherapeutic INR, but also prior to high-risk surgery or interventions. In patients with substantially elevated INRs, supplementation of vitamin K1 leads to a more rapid decline of the INR than just withholding of the vitamin K antagonist. Depending on the clinical situation, vitamin

K1 may be given as an oral or i.v. preparation. Subcutaneous or intramuscular applications are not recommended because of an unpredictable response and increased bleeding risk at the injection site. In the case of oral vitamin K1 administration, study reports indicate that low-dose vitamin K1 (2.5 mg) is a safe and effective treatment also for severely over-anticoagulated nonbleeding patients. Limiting the dose of vitamin K1 to 1 mg to 2.5 mg will avoid overcorrection of the INR. Because all vitamin K antagonist treated patients harbour an intrinsic thrombotic risk, choosing the reversal strategy with minimal correction of the coagulation defect that provides maximal haemostatic effect represents a challenge. *(15)*

Therefore, it is particularly important to administer only as much phytomenadione as necessary to avoid temporary resistance to vitamin K antagonists, whereby oral administration is the simpler and more pleasant form of therapy compared to intravenous administration, which also saves on the use of health care professionals. Tablets have major disadvantages in this type of therapy. Firstly, the fixed-dose system imposes severe restrictions on the choice of dose. In particular, 10 mg tablets that cannot be divided are unsuitable for significantly lower dosages, so that excessive dosages could have a negative impact on patient safety. Secondly, patients with swallowing difficulties may face challenges and, thirdly, tablets appear to be available only in individual countries and not across the board.

This is not a concern with phytomenadione MM for intramuscular and intravenous injection or oral administration since any desired dosage can be applied due to the finely adjustable solution. Another advantage is that it contains a mixed micelle system that acts as its own transport system, whereas in the case of tablets, patients with deficiencies in bile acid production need to be given bile acids additionally.

In addition, the phytomenadione MM solution can be used without any concerns when tablets cannot be used for other reasons, e.g. when children or older people have difficulty swallowing.

8.4 Phytomenadione MM solution for injection and oral administration versus other phytomenadione formulations for injection

According to the “Public data from Article 57 database”, there are three additional phytomenadione containing formulations for injection authorised on the European market: Fitomenadion Terapia (Romania), Kanavit (Cyprus, Czech Republic and Slovakia) and Vitacon (Poland) *(42, 44-46)*. None of them contains a mixed micelle system but other solvents/emulsifiers and preservatives like polysorbate 80, propylene glycol, Cremophor EL, phenol or benzyl alcohol. The vitamin K1 preparation from Pfizer (non-EU) also contains an emulsifier (polyoxyethylated fatty acid derivative) and the preservative benzyl alcohol *(47)*.

The ingredients of the comparator products can be considered critical for parenteral administration. Both Polysorbate 80 and Cremophor EL are known to trigger anaphylactoid reactions *(48, 49)*. In a comparative study between phytomenadione Cremophor EL and phytomenadione MM, this negative property of Cremophor EL has already been proven *(35)*. Propylene glycol is known to cause pain on injection, inflammation and haemolyses *(50)*. Injecting preservatives can also lead to adverse effects. Phenol, for example, is highly toxic *(50)*. Benzyl alcohol has been associated with toxicity in newborns and has been reported to be associated with a fatal "Gasping Syndrome" in premature infants *(47)*. For these reasons, the USPI for the Pfizer/Hospira product includes a black boxed warning, referring to severe reactions, including fatalities after intravenous and intramuscular injections. Therefore, the intravenous and intramuscular routes should be restricted to those situations where the subcutaneous route is not feasible, and the serious risk involved is considered justified *(47)*. Additionally, the

European Medicine Agency lists benzyl alcohol in the annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', including warnings regarding allergic reactions and the possibility to harm young children *(51)*.

In summary, it can be assumed that injections of phytomenadione MM are better tolerated and therefore safer for patients because the special mixed micelle system makes it possible to avoid both emulsifiers and preservatives and therefore anaphylactoid reactions when injected. Since some of these formulations can also be taken orally, there is an additional advantage for phytomenadion MM: it contains a mixed micelle system that acts as its own transport system, whereas in the case of the other formulations, patients with deficiencies in bile acid production need to be given bile acids additionally.

8.5 Comparison of intramuscular and oral phytomenadione MM for the prophylaxis of haemorrhagic disease of the newborn

Phytomenadione MM for the prophylaxis of haemorrhagic disease of the newborn can be administered both intramuscularly and orally. While an intramuscular injection of 1 mg phytomenadione MM immediately after birth is sufficient, babies with oral prophylaxis must be treated two to three times with 2 mg phytomenadione MM each time (immediately after birth, after 4-7 days and, for children who are fully breastfed, after 1 month) *(1)*. The intramuscular dosage regime is based on its depot characteristic and the continued release of phytomenadione, which allows a single dose *(52)*. A single dose of 1 mg intramuscular vitamin K is considered the gold standard because it consistently prevents most cases of late VKDB and is more effective than three 1 mg or 2 mg oral doses *(9)*. It further eliminates potential risks associated with oral dosing regimens, including incomplete compliance to repeated dosing and vitamin K malabsorption in babies with cholestasis *(9)*.

In conclusion, a single intramuscular injection is safer, particularly in preterm or term neonates at special risk (see 7.1) and in regions with limited health care or access to health care, where there is a risk of incomplete oral prophylaxis. On the other hand, babies can be effectively protected by the oral regime if parents refuse invasive intramuscular administration.

9. Summary of recommendations in current clinical guidelines

9.1 Phytomenadione MM paediatric 2 mg/0.2 mL

Due to the insufficient vitamin K levels in newborns, it is strongly recommended to administer vitamin K for the prophylaxis of haemorrhagic disease. With this almost all cases of VKDB can be prevented by phytomenadione prophylaxis given to the newborn *(8, 9)*.

Thus, the medical need of vitamin K prophylaxis in newborns has been accepted worldwide. As a result, most developed countries have a policy to administer vitamin K to all newborn babies making VKDB now a rare life-threatening disease with a reduced incidence of late VKDB to approximately 1 case per 100.000 newborns *(8, 9)*. Therefore, almost all major clinical practice guidelines recommend routine administration of vitamin K after birth.

Examples for medicinal guidelines are:

- Germany: Prophylaxis of vitamin K deficiency bleeding (VKDB) in newborns *(53)*

- United Kingdom: Vitamin K prophylaxis for neonates, Postnatal Care *(54)*
- Canada: Guidelines for vitamin K prophylaxis in newborns *(5)*
- United States: Guidelines for vitamin K prophylaxis, vitamin K and the newborn infant *(55, 56)*
- New Zealand: Vitamin K prophylaxis for the newborn *(57)*
- India: Injection vitamin K prophylaxis at birth *(58)*
- International: WHO recommendations on newborn health *(59)*

Moreover, the NHS trust in the United Kingdom also recommends vitamin K prophylaxis to the neonates with special reference to the unique formulated phytomenadione MM paediatric *(54)*. This is also applicable in Germany *(53)*. Additionally, the Martindale lists phytomenadione MM as proprietary preparation in different counties *(60)*, and a standard textbook in Germany lists phytomenadione MM for the treatment of vitamin K deficiencies and as antidot to vitamin K antagonists *(61)*. The WHO has classified the active ingredient phytomenadione as an essential medicine in general *(13)*.

In conclusion, phytomenadione paediatric MM 2 mg/0.2 mL is a highly effective and easy-to-use medication that provides very effective protection against rare but potentially fatal haemorrhages. The focus is on the neonatal patient group, which is particularly worthy of protection. The consequences of haemorrhage in newborns who have not received the prophylaxis can be severe and include lifelong disabilities, the treatment of which would far exceed the costs of prophylaxis with phytomenadione MM paediatric.

9.2 Phytomenadione MM 10 mg/1 mL

In clinical practice as well as according to several clinical guidelines *(62-70)*, vitamin K is recommended in particular for the treatment of haemorrhagic complications associated with coumarin-type anticoagulants such as phenprocoumon, warfarin, and acenocoumarol. These vitamin K anticoagulants (VKAs) are the most frequently used anticoagulants for the prevention of thromboembolic complications of vascular diseases. The use of VKA is demanding and due to the narrow therapeutic window, regular monitoring of laboratory parameters is essential. Elevation of the INR, a measure of the intensity of anticoagulation, is an independent risk factor for major bleeding. Vitamin K therapy effectively corrects INR in patients with coumarin-associated coagulopathy. Accordingly, the WHO has classified the active ingredient phytomenadione as an essential medicine *(21)*.

In conclusion, the unique formulated phytomenadione MM is a highly effective and easy-to-use medication that is administered especially in life-threatening situations like severe bleeding. The consequences of haemorrhage due to VKA overdosed patient who cannot receive an antidote treatment by vitamin K may be severe and include lifelong disabilities, the treatment of which would far exceed the costs of treatment with phytomenadione MM.

10. Summary of available data on comparative cost and cost-effectiveness

Price of phytomenadione MM in available markets

The price range for the phytomenadione MM 2 mg/0.2 mL is between $0.26 and $3.00 (mean value $1.63) per ampoule, and for the phytomenadione MM 10 mg/1 mL, it ranges from $0.35 to $4.00 (mean value $2.18) per ampoule.

Average cost per patient and patients' exposure

The population eligible for the treatment with phytomenadione MM includes (1) neonates to prevent and treat VKDB and (2) adults with haemorrhage or risk of haemorrhage as a result of severe 'hypoprothrombinaemia' (i.e. deficiency of clotting factors II, VII, IX and X) of various aetiologies *(1, 14)*.

The number of patients exposed to phytomenadione MM post-authorisation was estimated based on the mass of phytomenadione sold (about 136 kg) and the assumption that the total treatment dose was 10 - 50 mg for adults and 1 - 6 mg for infants (depending on intramuscular or oral administration) *(71)*.

For the purpose of exposure calculation, an average dose of 4 mg in paediatric patients (phytomenadione MM 2 mg/0.2 mL) and 10 mg in adult patients (phytomenadione MM 10 mg/1 mL) was used. The assumptions for calculation were chosen in accordance to previous reports *(71)*.

These assumptions result in an average treatment cost of:

Table 3. Average treatment costs

Formulation	Mean dose	Needed number of ampoules	Mean price per ampoule	Price per dose
Phytomenadione MM 2 mg/0.2 mL	4 mg	2	$1.63	$3.26
Phytomenadione MM 10 mg/1 mL	10 mg	1	$2,18	$2.18

CHEPLAPHARM does not have access to the gender and age information for patients who have taken phytomenadione MM. The only available stratification is by formulation and by geography.

The mass of phytomenadione MM sold in European Economic Area (EEA) and the Rest of the world (RoW) is sourced from the sales volumes of CHEPLAPHARM. The sales data are provided on a monthly basis; therefore, cumulative exposure is available from the international birth date (IBD) to the data lock point (DLP), i.e. 31 December 2023.

The cumulative and interval patient exposures to the marketed phytomenadione MM formulations are listed in Table 4 and Table 5, respectively.

Table 4. Cumulative exposure from marketing experience from IBD to DLP (31 Dec 2023) *(71)*

Formulation	Patient group	Estimated number of patients (in million)
Phytomenadione MM 2 mg/0.2 mL	Paediatric	1 198
Phytomenadione MM 10 mg/1 mL	Adult	1 255
Total		**2 453**

Table 5. Interval exposure from marketing experience (Jan – Dec 2023) *(71)*

Formulation	Patient group	Region	Estimated number of patients (in million)
Phytomenadione MM 2 mg/0.2 mL	Paediatric	EEA	3 052 910
		RoW	3 300 597
		Total	**6 353 507**
Phytomenadione MM 10 mg/1 mL	Adult	EEA	6 817 140
		RoW	4 288 315
		Total	**11 105 455**
Total		EEA	9 870 050
		RoW	7 588 913
		Total	**17 458 963**

In the reporting interval from 1 January 2023 to 31 December 2023, an estimated total of about 17.5 million patients received phytomenadione MM *(71)*.

Volume of sales

From 2020 to the first half of 2024 (2024 H1) phytomenadione MM was marketed as presented in table 6.

Table 6. The sales volume of phytomenadione MM in available markets from 2020 to 2024

Country/ Area	Phytomenadione MM 2 mg/0.2 mL (1000, ampoule)					Phytomenadione MM 10 mg/1 mL (1000, ampoule)				
	2020	2021	2022	2023	2024 H1	2020	2021	2022	2023	2024 H1
Argentina	—	—	—	—	—	47	57	45	46	20
Australia	330	347	331	325	189	113	121	133	124	87
Austria	259	252	230	231	109	143	130	119	119	46
Belarus	15	19	23	34	15	14	18	29	30	11
Belgium	310	289	268	214	102	183	171	165	162	83
Bulgaria	—	—	—	—	—	36	40	46	59	15
Chile	—	—	—	—	—	7	9	8	9	4
Colombia	4	1	0	3	2	0	0	1	0	0
Croatia	—	—	—	—	—	141	142	130	133	66
Ecuador	—	—	—	—	—	3	0	0	0	0
Egypt	—	—	—	—	—	1	0	0	0	0
Estonia	0	0	2	2	0	—	—	—	—	—
Finland	—	—	—	—	—	81	79	75	64	35
Germany	2028	2049	2000	1846	865	1657	1524	1579	1413	711
Greece	—	—	—	—	—	87	60	16	35	19
Hong Kong	52	43	34	36	7	112	99	100	95	0
Hungary	506	541	516	517	237	133	65	55	51	22
Ireland	74	80	71	70	17	34	35	34	29	16
Italy	507	461	390	331	157	2127	1756	1429	1357	630
Kuwait	32	29	32	19	5	—	—	—	—	—
Latvia	5	3	1	1	0	3	0	0	0	0
Lebanon	3	2	0	0	0	—	—	—	—	—
Luxembourg	6	1	1	1	0	—	—	—	—	—
Morocco	—	—	—	—	—	121	108	78	96	50
Netherlands	58	53	32	30	13	38	30	17	16	5

New Zealand	82	81	75	48	23	21	20	25	14	8
Norway	66	71	65	65	33	8	8	9	8	3
Peru	—	—	—	—	—	28	0	13	31	3
Philippines	—	—	—	—	—	128	101	110	97	26
Poland	131	89	71	56	21	—	—	—	—	—
Portugal	69	66	72	72	33	91	93	87	87	45
S. Africa	1764	2697	2411	2135	960	876	1363	1297	1201	694
Saudi Arabia	147	110	245	324	146	114	95	263	131	84
Serbia	52	67	70	63	36	75	77	77	56	34
Singapore	30	0	0	0	0	12	0	0	0	0
Slovenia	23	19	19	18	8	27	23	29	34	15
Spain	276	211	232	229	120	2114	2107	2145	1864	923
Sweden	—	—	—	—	—	127	123	117	113	55
Switzerland	127	131	119	122	61	80	85	77	68	26
Thailand	—	—	—	—	—	37	36	41	31	11
Turkey	1	1	0	0	0	1	1	0	0	0
UAE	79	75	75	86	39	73	35	48	39	27
UK	926	494	428	397	188	354	195	179	160	69
Uruguay	—	—	—	—	—	39	44	40	43	22
West Africa	—	—	—	—	—	1	0	0	0	0

Note: The data was sourced from the external service provider IQVIA.

Published economic articles - data sources and searches

Pubmed and Embase databases were searched for studies published from inception to September 2024. The search strategy included phytonadione, and the related generic name and brand name (e.g., vitamin K1, phytomenadione, and Konakion), as well as economics evaluation methods (e.g., cost-effectiveness analysis [CEA], cost-utility analysis [CUA], cost-minimisation analysis [CMA], cost-benefit analysis [CBA], and Health Technology Assessment [HTA]). Duplicate studies were eliminated, and titles and abstracts were screened according to the eligibility criteria mentioned below by two independent reviewers. We also searched the reference lists of relevant systematic reviews for additional articles.

English-language studies were included if they were: focused on vitamin K1 mixed-micellar injection for patients with VKDB; and provided information on economic evaluation, such as HTA or CEA. We excluded editorials, comments, and guidelines.

Published economic articles - study selection

A total of 8 potentially eligible articles were retrieved. Of these, 1 was excluded because of duplication, and 6 were excluded due to the title or abstract being irrelevant to the topic, mainly including parenteral nutrition, dosage form selection, detoxification, osteoporosis, and fracture. The remaining 1 article is summarised below *(72)*.

The objective of the study was to assess the management and outcomes of excessive anticoagulation in a group model health maintenance organisation, to compare management with the published guidelines, and to analyse the cost of treatment strategies.

The outcome of the study was, that the treatment with phytomenadione was 7 times more costly, than conservative treatment (temporary withdrawal of warfarin treatment).

However, this study was conducted in 1998. Since then, there have been improvements in treatment of patients with excessive coagulation resulting in better cost effectiveness both for conservative

treatment and phytomenadione treatment. Furthermore, the study was not focused on treatment with phytomenadione MM formulation but referred to a general treatment with phytomenadione including all formulations.

So, it can be argued that this study is not representative of cost effectiveness and current treatment guidelines for excessive coagulation because the data are outdated. Additionally, this study is not applicable for treatment with phytomenadione MM formulation because it was not analysed specifically.

11. Regulatory status, market availability and pharmacopeial standards

Regulatory status

CHEPLAPHARM Arzneimittel GmbH holds active registrations for phytomenadione MM products in more than 40 different countries. Furthermore, a product registration in China is currently ongoing. Please refer to Table 8 for more detailed information. The product is marketed under the international trade name Konakion. However, the trade name may vary in the different countries. Additionally, the product is provided via special license to several more markets (see Table 7 for more information). Furthermore, the product is provided to non-profit organszations such as UNICEF and Médicins Sans Frontières.

Table 8: Worldwide marketing authorization status of Konakion 2 mg/0.2 mL, 10 mg/1 mL (phytomenadione MM) (as of 31-Oct-2024)

Country	Registration Name	Strength	License number	MAH(s)	Marketing status
Argentina	Konakion MM	10 mg	44.649	CHEPLAPHARM	marketed
Australia	Konakion MM paediatric	2 mg	AUST R 71758	Pharmaco AU	marketed
Australia	Konakion MM	10 mg	AUST R 61654	Pharmaco AU	marketed
Austria	Konakion 2 mg/0,2 ml Mischmizellenlösung - Ampullen	2 mg	1-20786	CHEPLAPHARM	marketed
Austria	Konakion 10 mg/1 mL Mischmizellenlösung Ampullen	10 mg	1-18712	CHEPLAPHARM	marketed
Belgium	Konakion paediatric 2 mg/0,2 ml oplossing voor injectie en drank	2 mg	BE175813	CHEPLAPHARM	marketed
Belgium	Konakion 10 mg/1 mL oplossing voor injectie en drank	10 mg	BE055221	CHEPLAPHARM	marketed

Country	Registration Name	Strength	License number	MAH(s)	Marketing status
Chile	Konakion MM	10 mg	F-1176	Biopas	marketed
Colombia	Konakion MM pediátrico	2 mg	INVIMA 2023M-005453-R3	CHEPLAPHARM	marketed
Colombia	Konakion MM	10 mg	INVIMA 2023M-011075-R3	CHEPLAPHARM	marketed
Croatia	Konakion MM 10 mg/ml otopina za injekciju	10 mg	HR-H-364029156	CHEPLAPHARM	marketed
Denmark	Konakion Novum	2 mg	01612	CHEPLAPHARM	marketed
Denmark	Konakion Novum	10 mg	01612	CHEPLAPHARM	marketed
Finland	Konakion Novum 10 mg/ml injektioneste, liuos	10 mg	9542	CHEPLAPHARM	marketed
France	Vitamine K1 CHEPLAPHARM 2 mg/0,2 ml NOURRISSONS, solution buvable et injectable	2 mg	NL 23535 CIS 64337140	CHEPLAPHARM	marketed
France	Vitamine K1 CHEPLAPHARM 10 mg/1 mL, solution buvable et injectable	10 mg	NL 14399 CIS 60770621	CHEPLAPHARM	marketed
Germany	Konakion MM 2 mg	2 mg	42976.00.00	CHEPLAPHARM	marketed
Germany	Konakion MM 10 mg	10 mg	6044486.00.00	CHEPLAPHARM	marketed
Hong Kong	Konakion MM 2mg/0.2ml paediatric	2 mg	HK-38859	DKSH Hong Kong	marketed
Hong Kong	Konakion MM	10 mg	HK-30412	DKSH Hong Kong	marketed
Hungary	Konakion 2 mg/0,2 ml paediatric oldatos injekció	2 mg	OGYI-T-4204/03	CHEPLAPHARM	marketed, Special licence
Hungary	Konakion 10 mg/1 mL oldatos injekció	10 mg	OGYI-T-4204/02	CHEPLAPHARM	marketed, Special licence
Ireland	Konakion MM Paidiatric 2 mg/0.2 mL oral solution or solution for injection	2 mg	PA 2239/002/002	CHEPLAPHARM	marketed
Ireland	Konakion MM Ampoules 10 mg/1 mL Solution for injection and oral solution	10 mg	PA 2239/002/001	CHEPLAPHARM	marketed

Country	Registration Name	Strength	License number	MAH(s)	Marketing status
Israel	Konakion MM 2 mg/0.2 mL paediatric	2 mg	No.105-47-28944-00	Tzamal/Bio-Pharma	marketed
Israel	Konakion MM	10 mg	No.062-28-21477-00	Tzamal/Bio-Pharma	marketed
Italy	Konakion prima infanzia 2 mg/0,2 ml soluzione orale e iniettabile	2 mg	AIC n°008776066	CHEPLAPHARM	marketed
Italy	Konakion 10 mg/ml	10 mg	AIC n°008776078	CHEPLAPHARM	marketed
Jordan	Konakion MM Paediatric	2 mg	297/ND/1997	CHEPLAPHARM	marketed
Jordan	Konakion MM	10 mg	20/ND/1997	CHEPLAPHARM	marketed
Kenya	Konakion MM Paediatric	2 mg	10728	CHEPLAPHARM	marketed
Kenya	Konakion MM	10 mg	2029	CHEPLAPHARM	marketed
Kuwait	Konakion MM Ampoules 2mg/0.2ml Paediatric	2 mg	326	CHEPLAPHARM	marketed
Lebanon	Konakion MM pediatric 2 mg/0,2 ml	2 mg	171218/1	CHEPLAPHARM	marketed
Malta	Konakion MM Paidiatric 2 mg/0.2 mL oral solution or solution for injection	2 mg	AA1411/01901	EJ Busuttil Ltd	marketed
Malta	Konakion MM Ampoules 10 mg/1 mL Solution for injection and oral solution	10 mg	AA1456/00101	CHEPLAPHARM	marketed
Morocco	Konakion MM 2 mg/0,2ml	2 mg	63/2020DMP/21/NTTd	Bottu S.A.	marketed
Morocco	Konakion MM	10 mg	378/12DMP/21/NRQ	Bottu S.A.	marketed
Netherlands	Konakion MM voor kinderen 2 mg/0,2 ml oplossing voor injectie en oraal gebruik	2 mg	RVG 03809	CHEPLAPHARM	marketed
Netherlands	Konakion mixed micelles, 10 mg/ml oplossing voor injectie en oraal gebruik	10 mg	RVG 03808	CHEPLAPHARM	marketed
New Zealand	Konakion MM Paediatric	2 mg	TT50-3552/3	PharmacoNZ	marketed

Country	Registration Name	Strength	License number	MAH(s)	Marketing status
New Zealand	Konakion MM	10 mg	TT50-3552/2	PharmacoNZ	marketed
Norway	Konakion Novum 10 mg/ml injeksjonsvæske, oppløsning	2 mg	3280	CHEPLAPHARM	marketed
Oman	Konakion-MM Paediatric 2mg/0.2ml solution for oral use or im/iv injection	2 mg	D04261A	CHEPLAPHARM	marketed
Peru	Konakion MM	10 mg	EE-00729	Biopas	marketed
Philippines	Konakion MM 10 mg/mL i.v.	10 mg	DR-XY2508	Zuellig Pharma	marketed
Portugal	Kanakion MM pediátrico solução injetável	2 mg	8969824	CHEPLAPHARM	marketed
Portugal	Kanakion MM 10 mg/1 mL solução injectável	10 mg	8969832	CHEPLAPHARM	marketed
Saudi Arabia	Konakion MM paediatric	2 mg	4-5444-21	CHEPLAPHARM	marketed
Saudi Arabia	Konakion MM 10mg/ml amp I.V.	10 mg	5-5444-21	CHEPLAPHARM	marketed
Serbia	Konakion MM, 2 mg/0.2 mL, rastvor za injekciju	2 mg	515-01-00530-23-001	Clinres	marketed
Serbia	Konakion MM, 10 mg/1 mL, rastvor za injekciju	10 mg	515-01-00531-23-001	Clinres	marketed
South Africa	Konakion MM Paediatric	2 mg	29/22/0492	Pharmaco Distribution (Pty) Ltd.	marketed
South Africa	Konakion MM 10 mg/1 mL	10 mg	H2250	Pharmaco Distribution (Pty) Ltd.	marketed
Spain	Konakion 2 mg/0,2 ml pediátrico solución oral/solución inyectable	2 mg	21.610	CHEPLAPHARM	marketed
Spain	Konakion 10 mg/ml solución oral/solución inyectable	10 mg	27.262	CHEPLAPHARM	marketed
Sudan	Konakion MM 10mg/1ml (Vitamin K_1)	10 mg	INJ/09/229	CHEPLAPHARM	marketed
Sweden	Konakion Novum 10 mg/ml injektionsvätska, lösning	10 mg	10950	CHEPLAPHARM	marketed

Country	Registration Name	Strength	License number	MAH(s)	Marketing status
Switzerland	Konakion MM paediatric	2 mg	48112	CPS Cito Pharma Services GmbH	marketed
Switzerland	Konakion MM	10 mg	48112	CPS Cito Pharma Services GmbH	marketed
Thailand	Konakion MM	10 mg	1C 86/61	DKSH	marketed
Turkey	Konakion MM 2 mg/0.2 mL pediatrik ampul	2 mg	14611	Academy Anatolia	Marketed via special license
Turkey	Konakion MM 10 mg/ml ampul	10 mg	14610	Academy Anatolia	Marketed via special license
United Arab Emirates	Konakion MM paediatric 2mg	2 mg	22849-12-12426	CHEPLAPHARM	marketed
United Arab Emirates	Konakion MM 10mg	10 mg	22849-12-4792	CHEPLAPHARM	marketed
United Kingdom	Konakion MM Paediatric 2 mg/0.2 mL solution for injection; Phytomenadione 2 mg/0.2 mL solution for injection	2 mg	PL 45043/0041	Neon Healthcare Ltd	marketed
United Kingdom	Konakion MM Ampoules 10 mg/ml solution for injection; Phytomenadione 10 mg/1 mL solution for injection	10 mg	PL 45043/0040	Neon Healthcare Ltd	marketed
Uruguay	Konakion	10 mg	32265	CHEPLAPHARM	marketed

Product availability

Data on product availability are not readily available because there are several companies marketing this medicine. These data are not available to our company.

The countries were CHEPLAPHARM Arzneimittel GmbH is license holder are all fully stocked according to their demands. Furthermore, it is made sure, that the special license markets and non-profit organisations are also provided with this medicine. As phytomenadione is an essential medicine it is of utmost importance to our company to avoid out of stock situations to protect patient safety and health.

Pharmacopeial Standards

Phytomenadione is included in several pharmacopoeias including USP (United States Pharmacopoeia), Ph.Eur. (European Pharmacopoeia) and JP (Japanese Pharmacopoeia).

12. References

1. CHEPLAPHARM Arzneimittel GmbH. Company Core Data Sheet 8.0 Konakion® MM 2 mg/0.2 ml paediatric. 2017 (-).
2. Van Winckel M, De Bruyne R, Van De Velde S, Van Biervliet S. Vitamin K, an update for the paediatrician. Eur J Pediatr. 2009;168(2):127-34 (https://doi.org/10.1007/s00431-008-0856-1).
3. Eden RE, Daley SF, Coviello JM. Vitamin K Deficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024: (https://www.ncbi.nlm.nih.gov/books/NBK536983/).
4. Shearer MJ, Fu X, Booth SL. Vitamin K nutrition, metabolism, and requirements: current concepts and future research. Adv Nutr. 2012;3(2):182-95 (https://doi.org/10.3945/an.111.001800).
5. Ng E, Loewy AD. Position Statement: Guidelines for vitamin K prophylaxis in newborns: A joint statement of the Canadian Paediatric Society and the College of Family Physicians of Canada. Can Fam Physician. 2018;64(10):736-9 (https://www.cfp.ca/content/64/10/736.long).
6. Marchili MR, Santoro E, Marchesi A, Bianchi S, Rotondi Aufiero L, Villani A. Vitamin K deficiency: a case report and review of current guidelines. Ital J Pediatr. 2018;44(1):36 (https://doi.org/10.1186/s13052-018-0474-0).
7. McNinch AW, Upton C, Samuels M, Shearer MJ, McCarthy P, Tripp JH et al. Plasma concentrations after oral or intramuscular vitamin K1 in neonates. Arch Dis Child. 1985;60(9):814-8 (https://doi.org/10.1136/adc.60.9.814).
8. Busfield A, Samuel R, McNinch A, Tripp JH. Vitamin K deficiency bleeding after NICE guidance and withdrawal of Konakion Neonatal: British Paediatric Surveillance Unit study, 2006-2008. Arch Dis Child. 2013;98(1):41-7 (https://doi.org/10.1136/archdischild-2011-301029).
9. Zurynski Y, Grover CJ, Jalaludin B, Elliott EJ. Vitamin K deficiency bleeding in Australian infants 1993-2017: an Australian Paediatric Surveillance Unit study. Arch Dis Child. 2020;105(5):433-8 (https://doi.org/10.1136/archdischild-2018-316424).
10. Burke M, Bernhardt H, Reith DM, Barker D, Broadbent RS, Wheeler BJ. Perinatal influences on the uptake of newborn Vitamin K prophylaxis--a retrospective cohort study. Aust N Z J Public Health. 2015;39(6):573-6 (https://doi.org/10.1111/1753-6405.12399).
11. Khambalia AZ, Roberts CL, Bowen JR, Nassar N. Maternal and infant characteristics by mode of vitamin K prophylaxis administration. J Paediatr Child Health. 2012;48(8):665-8 (https://doi.org/10.1111/j.1440-1754.2012.02448.x).
12. Sahni V, Lai FY, MacDonald SE. Neonatal vitamin K refusal and nonimmunization. Pediatrics. 2014;134(3):497-503 (https://doi.org/10.1542/peds.2014-1092).
13. WHO Model List of Essential Medicines for Children - 9th list [website]. 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.03).
14. CHEPLAPHARM Arzneimittel GmbH. Company Core Data Sheet 5.0 Konakion® MM 10 mg/01 ml paediatric. 2017 (-).
15. Eichinger S. Reversing vitamin K antagonists: making the old new again. Hematology Am Soc Hematol Educ Program. 2016;2016(1):605-11 (https://doi.org/10.1182/asheducation-2016.1.605).
16. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. Cmaj. 2008;179(3):235-44 (https://doi.org/10.1503/cmaj.080171).
17. van Geest-Daalderop JH, Sturk A, Levi M, Adriaansen HJ. Omvang en kwaliteit van de antistollingsbehandeling met cumarinederivaten door de Nederlandse trombosediensten. [Extent and quality of anti-coagulation treatment with coumarin derivatives by the Dutch Thrombosis Services]. Ned Tijdschr Geneeskd. 2004;148(15):730-5 (https://pubmed.ncbi.nlm.nih.gov/15119208/).

18. Pengo V, Denas G. Optimizing quality care for the oral vitamin K antagonists (VKAs). Hematology Am Soc Hematol Educ Program. 2018;2018(1):332-8 (https://doi.org/10.1182/asheducation-2018.1.332).
19. Steinberg BA, Blanco RG, Ollis D, Kim S, Holmes DN, Kowey PR et al. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II: rationale and design of the ORBIT-AF II registry. Am Heart J. 2014;168(2):160-7 (https://doi.org/10.1016/j.ahj.2014.04.005). Licence: NIHMS618026.
20. Bon usage des médicaments antivitamine K (AVK). Agence Nationale de Sécurité du Médicament et des produits de santé; 1212 (https://archive.ansm.sante.fr/content/download/6187/59989/version/12/file/Bon+usage+AVK+actualis%C3%A9e+juillet+2012.pdf).
21. WHO Model List of Essential Medicines - 23rd list [website]. 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02).
22. Greer FR, Marshall SP, Severson RR, Smith DA, Shearer MJ, Pace DG et al. A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. Arch Dis Child. 1998;79(4):300-5 (https://doi.org/10.1136/adc.79.4.300).
23. Schubiger G, Grüter J, Shearer MJ. Plasma vitamin K1 and PIVKA-II after oral administration of mixed-micellar or cremophor EL-solubilized preparations of vitamin K1 to normal breast-fed newborns. J Pediatr Gastroenterol Nutr. 1997;24(3):280-4 (https://doi.org/10.1097/00005176-199703000-00009).
24. Amédée-Manesme O, Lambert WE, Alagille D, De Leenheer AP. Pharmacokinetics and safety of a new solution of vitamin K1(20) in children with cholestasis. J Pediatr Gastroenterol Nutr. 1992;14(2):160-5 (https://doi.org/10.1097/00005176-199202000-00007).
25. von Kries R, Hachmeister A, Göbel U. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. Arch Dis Child Fetal Neonatal Ed. 2003;88(2):F109-12 (https://doi.org/10.1136/fn.88.2.f109).
26. B-159-050: Comparative bioavailability and kinetics of KONAKION MM; Ro 01-6722/120, oral and parenteral in infants suffering from chronic cholestasis. F. Hoffmann-LA Roche Ltd; 1991 (-).
27. B-115-018: Tolerability of Ro 01-6722/120 in infants with stable cholestasis. F. Hoffmann-LA Roche Ltd; 1985 (-).
28. B-117-130: Pharmacokinetics of a single dose of vitamin (10 mg) mixed micelles solution administered intramuscularly to 4 cholestatic babies. F. Hoffmann-LA Roche Ltd; 1987 (-).
29. B-115-046: Bioavailability and efficacy of KONAKION MM Ro 01-6722/130, 1.5 mg vitamin K1 i.m. versus 3.0 mg vitamin K1 oral in healthy new-born breast-fed babies. F. Hoffmann-LA Roche Ltd; 1990 (-).
30. B-115-048: Bioavailability of KONAKION MM, Ro 01-6722/130, oral and parenteral in mature neonates at birth (> 2000 g) and the evolution of vitamin K1 plasma level in breast-fed babies. F. Hoffmann-LA Roche Ltd; 1990 (-).
31. B-159-051: Efficacy and tolerability of KONAKION MM 2 mg vitamin K1 orally versus 1 mg vitamin K1 intramuscularly in new-born, breast-fed babies. F. Hoffmann-LA Roche Ltd; 1992 (-).
32. B-162-000: Randomized comparative trial to evaluate efficacy and tolerability of KONAKION MM, Ro 01-6722/135, KONAKION drops Ro 01-6722/070 orally and KONAKION ampoules Ro 01-6722/119 intramuscularly in the prophylaxis of hemorrhagic disease in new-born, breast-fed infants. F. Hoffmann-LA Roche Ltd; 1993 (-).
33. B-162-001: Bioavailability and efficacy of KONAKION MM ampoules vs KONAKION drops in healthy new-born at term (>2000 g) breast-fed infants 2 mg per os. F. Hoffmann-LA Roche Ltd; 1993 (-).

34. B-162-002: Efficacy and tolerability of KONAKION MM Ro 01-6722/135 1 mg vitamin K1 i.v. and 2 mg vitamin K1 p.o. in the prophylactic treatment against hemorrhagic disease in premature infants. F. Hoffmann-LA Roche Ltd; 1993 (-).
35. Pereira SP, Williams R. Adverse events associated with vitamin K1: results of a worldwide postmarketing surveillance programme. Pharmacoepidemiol Drug Saf. 1998;7(3):173-82 (https://doi.org/10.1002/(sici)1099-1557(199805/06)7:3<173::Aid-pds343>3.0.Co;2-8).
36. Schubiger G, Tönz O, Grüter J, Shearer MJ. Vitamin K1 concentration in breast-fed neonates after oral or intramuscular administration of a single dose of a new mixed-micellar preparation of phylloquinone. J Pediatr Gastroenterol Nutr. 1993;16(4):435-9 (https://doi.org/10.1097/00005176-199305000-00016).
37. B-117-131: Comparative tolerability and efficacy study: vitamin mixed micelles solution versus vitamin solution containing Cremophor EL both administered in a single dose i.m., to babies suffering from chronic cholestasis. F. Hoffmann-LA Roche Ltd; 1987 (-).
38. B-115-040: Comparative tolerability of Ro 01-6722/120 (KONAKION MM) and Ro 01-6722/092 (KONAKION commercial form with Cremophor5 mg/0.5 ml i.m. in healthy new-born and premature babies. F. Hoffmann-LA Roche Ltd; 1989 (-).
39. Soedirman JR, De Bruijn EA, Maes RA, Hanck A, Grüter J. Pharmacokinetics and tolerance of intravenous and intramuscular phylloquinone (vitamin K1) mixed micelles formulation. Br J Clin Pharmacol. 1996;41(6):517-23 (https://doi.org/10.1046/j.1365-2125.1996.03847.x).
40. B 159-012: Bioavailability of three vitamin K1 preparations (Ro 01-6722 Konakion), cremophor /119, mixed micelles/131, and /141 relative to Tween 80/143 formulation (M10400/BK14677). F. Hoffmann-LA Roche Ltd; 1995 (-).
41. M 33230: Comparison of the bioavailabilities of Konakion MM 10 mg (Ro 01-6722/131) and Konakion N solution (Ro 01-6722/076) after oral administration of 10 mg of each. F. Hoffmann-LA Roche Ltd; 1998 (-).
42. Article 57 database [website]. (https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/data-medicines-iso-idmp-standards-post-authorisation/public-data-article-57-database).
43. drugs.com phytomenadione [website]. (https://www.drugs.com/pro/phytonadione-tablets.html).
44. Terapia. Summary of Product Characteristics. Fitomenadion Terapia. (-).
45. BB Pharma as. Summary of Product Characteristics. Kanavit. (-).
46. Zakłady Farmaceutyczne POLPHARMA S.A. Summary of Product Characteristics. Vitacon. (-).
47. Pfizer/Hospira. USPI. VITAMIN K1 INJECTION – Phytonadione Injectable Emulsion. (-).
48. Tang C, Zhao Y, Liu J, Zheng X, Guo X, Liu H et al. Polysorbate 80 as a possible allergenic component in cross-allergy to docetaxel and fosaprepitant: A literature review. J Oncol Pharm Pract. 2023;29(8):1998-2006 (https://doi.org/10.1177/10781552231203186).
49. Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35 868. Br J Anaesth. 1984;56(6):617-26 (https://doi.org/10.1093/bja/56.6.617).
50. Schmidt PC, Lang S, Pielenhofer J. Pharmazeutische Hilfsstoffe. 2. Auflage. Govi; 2020 (-).
51. Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668). 2024 (https://www.ema.europa.eu/en/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human-use#document-history-revision-3-66675).
52. Loughnan PM, McDougall PN. Does intramuscular vitamin K1 act as an unintended depot preparation? J Paediatr Child Health. 1996;32(3):251-4 (https://doi.org/10.1111/j.1440-1754.1996.tb01564.x).
53. Prophylaxis of vitamin K deficiency bleeding (VKDB) in newborns. Registration number 024/022. In revision. AWMF; 2016 (https://register.awmf.org/assets/guidelines/024-022l_S2k_Prophlaxe_Vitamin_K_Mangel_Neugeborene_2016-04-abgelaufen.pdf).

54. Vitamin K prophylaxis for neonates. NHS; 2024 (https://www.clinicalguidelines.scot.nhs.uk/nhsggc-guidelines/nhsggc-guidelines/neonatology/vitamin-k-prophylaxis-for-neonates/).
55. Guidelines for Vitamin K Prophylaxis. Stanford medicine; 2006 (https://med.stanford.edu/newborns/clinical-guidelines/vitamink.html).
56. Hand I, Noble L, Abrams SA. Vitamin K and the Newborn Infant. American acadamy of paediatrics; 2022 (https://publications.aap.org/pediatrics/article/149/3/e2021056036/184866/Vitamin-K-and-the-Newborn-Infant).
57. Vitamin K Prophylaxis for the Newborn. New Zealand College of midwifes; 2016 (https://www.midwife.org.nz/wp-content/uploads/2019/05/Vitamin-K-Prophylaxis-for-the-Newborn.pdf).
58. Injection Vitamin K Prophylaxis at Birth (in facilities). Ministry of Health and Family Welfare Government of India - Child Health Division; 2014 (https://nhm.gov.in/images/pdf/programmes/child-health/guidelines/Vitamin_K_Operational_Guidelines.pdf).
59. WHO recommendations on newborn health. World Health Organization; 2017 (https://iris.who.int/bitstream/handle/10665/259269/WHO-MCA-17.07-eng.pdf;jsessionid=CF264F9448EAE361B5BE63F6B8BD284B?sequence=1).
60. Sweetman SC. Martindale - The Complete Drug Reference. 36th edition. Pharmaceutical Press; 2009 (-).
61. Geisslinger G. Mutschler Arzneimittelwirkungen. 11th edition. Wissenschaftliche Verlagsgesellschaft Stuttgart; 2020 (-).
62. De Caterina R, Husted S, Wallentin L, Agnelli G, Bachmann F, Baigent C et al. Anticoagulants in heart disease: current status and perspectives. Eur Heart J. 2007;28(7):880-913 (https://doi.org/10.1093/eurheartj/ehl492).
63. Dempfle CE, Borggrefe M. Vermeidung von Notfallsituationen bei gerinnungshemmender Therapie mit Vitamin-K-Antagonisten Ein praktischer Leitfaden zu Einstellung, Umstellung und Uberbrückung von Therapiepausen. [Avoiding emergency situations under anticoagulant therapy with vitamin K antagonists]. Internist (Berl). 2005;46(9):1006-10, 12-3 (https://doi.org/10.1007/s00108-005-1479-5).
64. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160s-98s (https://doi.org/10.1378/chest.08-0670).
65. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS. An update of consensus guidelines for warfarin reversal. Med J Aust. 2013;198(4):198-9 (https://doi.org/10.5694/mja12.10614).
66. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. J Am Coll Cardiol. 2003;41(9):1633-52 (https://doi.org/10.1016/s0735-1097(03)00416-9).
67. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C et al. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol. 2011;154(3):311-24 (https://doi.org/10.1111/j.1365-2141.2011.08753.x).
68. Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. Br J Haematol. 2013;160(1):35-46 (https://doi.org/10.1111/bjh.12107).
69. Douketis JD, Spyropoulos AC, Murad MH, Arcelus JI, Dager WE, Dunn AS et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest. 2022;162(5):e207-e43 (https://doi.org/10.1016/j.chest.2022.07.025).

70. Tazarourte K, Riou B, Tremey B, Samama CM, Vicaut E, Vigué B. Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study). Crit Care. 2014;18(2):R81 (https://doi.org/10.1186/cc13843).
71. CHEPLAPHARM Arzneimittel GmbH. Periodic Benefit Risk Evaluation Report for Konakion. 2024 (-).
72. Lousberg TR, Witt DM, Beall DG, Carter BL, Malone DC. Evaluation of excessive anticoagulation in a group model health maintenance organization. Arch Intern Med. 1998;158(5):528-34 (https://doi.org/10.1001/archinte.158.5.528).