Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

(PHYTOMENADIONE)

KONAKION® MM
KA-VIT

LV/W/0002/pdWS/001

Rapporteur:	Latvia
Finalisation procedure (day 120):	17.12.2012.
Date of finalisation of PAR	28.02.2013.

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	KONAKION KA-VIT
INN (or common name) of the active substance:	Phytomenadione
MAHs:	See section VIII Roche InfectoPharm
Pharmaco-therapeutic group (ATC Code):	B02BA01
Pharmaceutical form(s) and strength(s):	Solution for oral use Solution for injection 1 mg/0.1 ml

I. EXECUTIVE SUMMARY

Phytomenadione in paediatric population is licensed for prophylaxis and treatment of vitamin K deficiency bleeding (VKDB) in newborns and infants. Vitamin K deficiency bleeding can cause potentially lethal haemorrhagic disease in infancy and occurs in three different forms – early, classic and late. Current dosing recommendations for prophylaxis successfully eliminate early and classic VKDB, but the most appropriate regimen for prophylaxis of late VKDB is still searched. There is a variety of recommendations and practices in European countries.
In addition, in some Member States phytomenadione is authorized for treatment of coumarin anticoagulant overdose bleeding both in children and adults.

The preliminary assessment report with a list of questions to the MAHs was circulated in March 2012, additional requests for information were received from several Member States. The Applicants were asked to provide further information on phytomenadione safety aspects regarding reported association of i.m. vitamin K and childhood leukemia, additional studies on the optimal dosage for treatment of vitamin K deficiency bleeding, evidence on the use and posology of vitamin K dosage in reversal of coumarin anticoagulation, the dosage in prophylaxis of haemorrhagic disease in newborns. The Applicant's response and assessment of available studies led to proposal of several variations in product information, therefore an updated assessment report was circulated in September 2012.
Several comments were received from Member States that led to implementation of more detailed dosing information in section 4.2 and cross-reference to section 5.1 to include information from paediatric studies.
Upon finalization of the procedure Rapporteur's overall conclusions and proposed changes in Product Information were endorsed by all concerned Member States.

SmPC and PL changes are proposed in sections 4.2 and 5.1.

Summary of outcome

☐ No change

☒ Change

☐ New study data

☐ New safety information

☒ Paediatric information clarified: sections 4.2, 5.1

☐ New indication

4.2 Posology and method of administration
Dosage and administration

Healthy neonates of 36 weeks gestation and older:
Either:

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 4-7 days of age. A further 2 mg oral dose should be given at 1 month after birth. In exclusively formula fed infants the third oral dose can be omitted.

Preterm neonates of less than 36 weeks gestation weighing 2.5kg or greater, and term neonates at special risk (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics): 1mg IM or IV 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 2.5kg: 0.4 mg/kg (equivalent to 0.04 ml/kg) IM or IV 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.

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

CAUTION: care is required when calculating and measuring the dose in relation to the baby's weight (10 times dosing errors are common).

Dosing information for preterm babies at birth for the prophylaxis of Vitamin K deficiency bleeding

Weight of the baby	Dose of vitamin K at birth	Injection volume
1 kg	0.4 mg	0.04 ml
1.5 kg	0.6 mg	0.06 ml
2 kg	0.8 mg	0.08 ml
2.5 kg	1 mg	0.1 ml
Over 2.5 kg	1 mg	0.1 ml

Further oral doses in breast-fed infants have been advised, but safety or efficacy data for these additional doses is limited (see section 5.1).

Section 5.1
Paediatric population
A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinaemia (idiopathic neonatal hepatitis - 17 patients, biliary atresia - 13, total parenteral nutrition cholestasis - 3, Alagille's syndrome -2, alpha 1 antitrypsin deficiency - 2, inspissated bile syndrome - 2, and 5 miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis). The pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease was compared.
Main outcome measures were serum concentrations of vitamin K1 and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar K1 1 mg intravenously or 2 mg orally. A comparison was also made between K1 levels 24 hours after oral K1 administration with those of 14 healthy newborns given the same dose.

Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K1 concentrations, indicative of subclinical vitamin K deficiency. Median serum K1 concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K1 but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K1 compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum K1 > 10 ng/ml.

The data from a retrospective study indicate that weekly oral prophylaxis was effective in the prevention of VKDB. A total of 507 850 live babies were born during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. Oral vitamin K prophylaxis at birth 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age. No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100000 (95% CI).

The following information to be included in PIL section 3:

<Phytomenadione> can be given to your child by injection into a vein or muscle or by mouth. How it is given will depend upon what the medicine is being used for and whether your baby was born prematurely.

Prevention of vitamin K deficiency bleeding
Healthy babies delivered at or nearly full term
These babies will be given either:
• A single injection (1 mg) either at birth or soon after, or
• By mouth (oral) a first dose (2 mg) at birth or soon after. This is followed by a second 2 mg dose after 4 to 7 days and third 2 mg dose at 1 month. In exclusively formula fed infants the third oral dose can be omitted.

Premature babies or full term babies at special risk of bleeding
• These babies will be given <phytomenadione> as an injection at birth or soon after.
• More injections may be given later if your baby is still at risk of bleeding.

Further doses:
• Babies who are given vitamin K by mouth and who are breast-fed (not given formula milk) may need more doses of vitamin K by mouth.
• Bottle-fed babies given the two doses of vitamin K by mouth may not need any more doses of vitamin K. This is because it is included in formula milk.

II. RECOMMENDATION

Following assessment of submitted studies and discussion among Member States it was concluded that several changes should be implemented in Product Information to clarify paediatric information.

III. INTRODUCTION

Two MAHs submitted 29 completed paediatric studies for phytomenadione, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.
InfectoPharm submitted 2 completed paediatric studies, Roche submitted 27 completed pediatric studies and 18 overviews on phytomenadione.

A short critical expert overview has also been provided.

Both MAHs stated that the submitted paediatric studies do not influence the benefit risk for phytomenadione and during the assessment procedure agreed to the following regulatory action: update of paediatric information in section 4.2 and 5.1.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product, and related PL wording

- Licensing position in different member states with comparison of local SPC and Company Cora Data Sheet provided by MAH Roche

- PSUR data from both MAHs.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Vitamin K is an essential cofactor for γ-glutamyl carboxylase enzymatic activity that catalyses the γ -carboxylation of specific glutamic acid residues in a subclass of proteins. Coagulation factors II, VII, IX, and X, and protein C, protein S, protein Z depend on the presence of vitamin K for their activity.
Newborns are at risk of developing vitamin K deficiency, and this coagulation abnormality can lead to bleeding. Transplacental transfer of vitamin K during pregnancy, and the storage of vitamin K in neonatal liver is very limited.

Vitamin K deficiency bleeding (VKDB) or haemorrhagic disease of the newborn can account for potentially lethal haemorrhagic disease in infancy and occurs in three different forms:
• An early form of VKDB, which occurs in the first 24 hours of life and is often severe, and may include intracranial and intra-abdominal haemorrhage or cephalic haematoma
• The classic form of VKDB, which occurs between 24 hours and 7 days of life and mainly presents as gastrointestinal haemorrhage
• The late form of VKDB which presents between 7 days and 6 months of life. It is particularly severe with morbidity/mortality of approximately 20-40%.

The following pharmaceutical formulations were used in the clinical studies:

- Mixed micellar (MM) Konakion formulation 1 mg/0.1 ml was used in most submitted studies,
- Konakion Cremophor formulation;
- Polysorbat 80% formulation (not specified).

Prior to year 1990 Konakion® formulation contained polyethoxylated castor oil (Cremophor) as solvent for the lipophilic molecule phytomenadione. This formulation allowed single-dose administration of 1 mg vitamin K1 by the i.m. route at birth but was implicated in the development of anaphylactoid reactions related to the presence of Cremophor as non-active ingredient in the formulation. Currently authorized formulation is mixed micellar (Konakion MM) formulation, containing the bile constituents glycocholic acid and lecithin. This was based on the notion that bile is a physiological solubiliser of vitamin K1 and is needed for the absorption of vitamin K1 from the gastrointestinal tract.

In accordance with originator's core company position (CDS) the documented indications are:

<u>Prophylaxis and treatment of haemorrhagic disease of the newborn.</u>
The dosage for <u>prophylaxis</u> in healthy neonates: 3 doses, 2 mg orally at birth, at 4 to 7 days, after 4 – 6 weeks.
A single 1 mg (0.1 ml) dose i.m. 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.
Exclusively breast-fed babies:
In addition to the recommendations for all neonates, 2 mg orally should be given after four to six weeks.
Neonates with special risk factors (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics):
- 1 mg i.m. or i.v. at birth or shortly after birth if the oral route is unsuitable.

- i.m. and i.v. doses should not exceed 0.4 mg/kg (equivalent to 0.04 ml/kg) in premature infants weighing less than 2.5 kg.
- The size 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.

Despite vast experience with vitamin K, there are still several questions, e.g., is repeated oral administration as effective as i.m. administration for the prophylaxis of VKDB, in particular late onset VKDB? Different dose regimens are used in different countries. What is the most effective oral regimen?
Although intramuscular administration is considered the most effective, it is associated with pain, besides in 1992 an association between i.m. vitamin K prophylaxis in neonates and later childhood leukemia was reported.
To date there is no randomized clinical trial comparing the efficacy of intramuscular and oral administration of vitamin K (with or without repeated doses), and the large number of newborns required make it unlikely to be performed.

Differences in existing product information
MAH Roche has submitted licensing position in different member states with comparison of local SPC and Company Cora Data Sheet. Local SPCs show different deviations from CDS, mostly minor. Depending on local recommendations for VKDB prophylaxis only oral or intramuscular prophylaxis is approved in some countries. In Belgium and Luxemburg it is recommended to continue oral prophylaxis 1 – 2 mg once a week in healthy newborns, if they received oral prophylaxis at birth and continue > 50% breastfeeding.
In France in case of exclusive or “quasi-exclusive” breast-feeding in addition to the 2 mg oral prophylaxis at birth it is recommended to administer 2 mg orally per week until the end of the exclusive breast-feeding.
The main difference from the CDS in UK, Ireland is the information for treatment of overdose with coumarin anticoagulants licensed for the paediatric formulation in both the UK and Ireland. Therefore section 4.2 contains more dosage information.
In UK, Ireland, Hungary further monthly 2 mg oral doses until formula feeding is introduced have been advised (in exclusively breast-fed babies who received oral Konakion at birth, at 4-7 days and at 1 month), with a remark that no safety or efficacy data exist for these additional doses.

IV.2 Non-clinical aspects

No non-clinical documentation was provided.

IV.3 Clinical aspects

1. Introduction

The MAHs submitted reports for:

Doc. Ref	Active Substance	Title
		Oral mixed micellar vitamin K for prevention of late vitamin K

		deficiency bleeding
		Weekly oral vitamin K prophylaxis in Denmark
34057	PHYTOMENADION	Comparative bioavailability and kinetics of Konakion MM: Ro 01-6722/122, oral and parenteral in infants suffering from chronic cholestasis
34058	PHYTOMENADION	Bioavailability and efficacy of Konakion MM Ro 01-6722/130, 1.5mg vitamin K1 i.m. versus 3.0mg vitamin K1 oral in healthy newborn breast-fed babies
34059	PHYTOMENADION	Bioavailability of Konakino MM, Ro 01-6722/130, oral and parenteral in mature neonates at birth (>2000g) and the evolution of vitamin K1 plasma level in breastfed babies
34060	PHYTOMENADION	Efficacy and tolerability of Konakion MM1mg vitamin K1 orally versus 1mg vitamin K1 intramuscularly in newborn breastfed babies
34061	PHYTOMENADION	Bioavailability and efficacy of Konakion MM ampoules vs Konakion drops in healthy newborn at term (>2000g) breastfed infants 2mg per os
34062	PHYTOMENADION	Randomized comparative trial to evaluate efficacy and tolerability of Konakion MM, Ro 01-6722/135, Konakion drops Ro 01-6722/119 intramuscularly in the prophylaxis of hemorrhagic disease in newbord, breastfed infants
34063	PHYTOMENADION	Comparative tolerability and efficacy study: vitamin K1 mixed micelles solution versus vitamin K1 solution containing Cremophor EL both administered in a single dose i.m. to babies suffering from chronic cholestasis
34065	PHYTOMENADION	Efficacy and tolerability of Konakion MM Ro 01-6722/135, 1mg vitamin K1 i.v. and 2mg vitamin K1 p.o. in the prophylactic treatment against hemorrhagic disease in premature infants
34066	PHYTOMENADION	Pharmacokinetics of a single dose of vitamin K1 (10mg) mixed micelles solution administered i.m. to four cholestatic babies
34046	PHYTOMENADION	A comparison of the effect of a single intramuscular injection of Konakion MM pediatric formulation (Ro 016722-139 or Konakion Cremophor (castor oil) formulation (Ro 016722-119) administered at birth on plasma Vitman K levels in healthy breastfed neonates at day 1 and 14 days after birth (protocol no. BP16063)
34047	PHYTOMENADION	Final Study Report: A Comparison of the effect of Oral Viatamin K1 (Ro-6722/139) and intramuscular vitamin K(Konakion tween 80 Ro 01-6722/143) in exclusively breast-fed neonates on PIVKA II plasma concentrations and prothrombin time.
34050	PHYTOMENADION	Plasma vitamin K1 and PIVKA-II levels in breast fed infants after repeated oral administration of Ro 01-6722/141 (2x0.25 mg vitamin K1).
34051	PHYTOMENADION	Plasma levels of vitamin K1 and PIVKA levels in breast fed infants after repeated oral administration of 0.5 mg vitamin K1.
34052	PHYTOMENADION	Plasma Vitamin K1 and PIVKA-II Levels in Breast Fed Infants after Oral Administration of Ro 01-6722/141 (0.25 mg Vitamin K1) at Birth.
		Intracerebral Hemorrhage due to Hemorrhagic Disease of the Newborn and Failure to Administer Vitamin K at Birth
		Neonatal vitamin K prophylaxis in Great Britain and Ireland: the impact of perceived risk and product licensing on effectiveness
		Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993–94 and 2001–02
		Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries
		Late haemorrhagic disease of the newborn
		Intracranial hemorrhage due to late hemorrhagic disease in two siblings.
		Serious and life-threatening bleeding in late vitamin K deficiency
		Intracranial hemorrhages due to late-type vitamin K deficiency

		bleeding
		Vitamin K deficiency bleeding presenting as impending brain herniation
		Life-threatening retroperitoneal hemorrhage due to late vitamin K deficiency
		Delayed vitamin K deficiency as a cause of bleeding: still a concern in the 21st century!
		Intracerebral hemorrhage despite prophylactic administration of vitamin K in infants

2. Clinical studies

CLINICAL STUDY No. 1 **"Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding"**

- **Description**
- **Methods**
  - Objective(s) – to estimate, whether the use of a mixed micellar vitamin K preparation improves the efficacy of the 3 x 2 mg oral vitamin K schedule (in comparison to other simple preparations)
  - Study design - nationwide active surveillance
  - Study population /Sample size - 3 138 695 neonatal patients in Germany in 1997-2000
  - Treatments – three oral doses of 2 mg mixed micellar vitamin K preparation
  - Outcomes/endpoints - The rate of confirmed VKDB (vitamin K-deficiency bleeding) between day 8 and week 12.

- **Results**

  - Recruitment/ Number analysed - 3 138 695 neonatal patients
  - Baseline data - Twenty nine reports met the case definition: seven had not received any vitamin K prophylaxis; for three, vitamin K prophylaxis was unknown; two had insufficient vitamin K prophylaxis for their age; 17 had been given the recommended doses. The mixed micellar preparation had been given to 7, other preparations to 9, and one had been given both. These cases did not differ with respect to the site of bleeding and cholestasis detected at bleeding. Estimates of the use of the mixed micellar preparation in birth hospitals and by paediatricians yielded 1 817 769 newborns exposed to the mixed micellar preparation and 1 320 926 newborns exposed to other preparations.
  - Efficacy results - The rate of late VKDB was 0.44:100 000 (95% 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. The data on the 3 x 2 mg regimen did not show a significant improvement in the efficacy of oral vitamin K prophylaxis with the mixed micellar preparation.

Late vitamin K deficiency bleeding (day 8 – week 12) in Germany 1997 - 2000				
Prophylaxis	1997	1998	1999	2000
Unknown	1	0	0	2
None	1	1	3	2
Insufficient for age				
Mixed micellar	0	1	0	0
Cremophor	1	0	0	0
As recommended				
Mixed micellar	1	1	2	3

Cremophor	3	2	1	2
Polysorbat 80	0	0	0	1
Cremophor + mixed micellar	0	0	1	0
Total	7	5	7	10

Discussion on clinical aspects
In 21 of 29 cases cholestasis was detected after the bleeding episode, caused by bile duct atresia, hypoplasia in 3 cases, homozygous alpha 1 antitrypsin deficiency, Byler's disease and sclerosing cholangitis. This study shows the decreased efficacy of oral vitamin K prophylaxis in patients with cholestasis, this is well known. The rate of late VKDB was only slightly lower with the mixed micellar preparation, if compared to the other older vitamin K preparations. The proportion of children with cholestasis was similar in all prophylaxis failure cases. There are some limitations in study design – one data source, the number of children exposed to mixed micellar or other preparations is not precise, because approximately 10% may have received intramuscular or subcutaneous prophylaxis.
No new safety signals were detected.

CLINICAL STUDY No. 2 **"Weekly oral vitamin K prophylaxis in Denmark""**

- **Description**
- **Methods**
  - Objective(s) – the efficacy of giving 2 mg phytomenadione on the first day of life followed by 1 mg phytomenadione weekly until 12 weeks of age, which is administered by parents.
  - Study design - observational study
  - Study population /Sample size - 396 000 neonatal patients who received oral prophylaxis.
  - Treatments - 2 mg phytomenadione on the first day of life followed by 1 mg phytomenadione weekly until 12 weeks of age as long as they are mainly breastfed.
  - Outcomes/endpoints - The rate of VKDB

- **Results**
  - Recruitment/ Number analysed - 396 000 neonatal patients
  - Efficacy results - No cases of late VKDB were revealed, i.e. the incidence was 0 to 0.9:100 000 (95% CI), indicating almost complete protection.

Discussion on clinical aspects
Due to the low incidence of late VKDB it can be concluded that continuous weekly oral prophylaxis was effective. No new safety signals were detected.

MAH (Roche) sponsored studies

CLINICAL STUDY No.3 "Comparative bioavailability and kinetics of KONAKION MM; Ro 01-6722/120, oral and parenteral in infants suffering from chronic cholestasis"

- **Description**
- **Methods**

- Objective(s) - to study the bioavailability and kinetics of vitamin K1 (KONAKION MM) given orally (20 mg vitamin K1, 2ml) to infants suffering from chronic cholestasis, compared to the i.m. administration (10 mg vitamin K1, 1 ml)
- Study design – open controlled study, single centre
- Study population /Sample size – 13 children with chronic cholestasis, 1 - 5 years of age
- Treatments – oral administration of 20 mg K1, compared to i.m. 10 mg K1

➢ **Results**

- The two peak values differences 3 hours after administration of KONAKION MM (1827 ng/ml for i.m., 10 mg K1 and 1797 for oral 20 ml K1) showed no statistically significant differences. 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 decrease of plasma concentrations of vitamin K1 was somewhat slow after oral administration in these cholestatic infants. This result confirms the hypothesis that vitamin K1 given orally in form of bile-salt-lecithin mixed- micelles promotes absorption of vitamin K when in vivo bile-salts are absent.

Discussion on clinical aspects

The average body weight was 11.6 kg (ranging from 4.2 kg to 29 kg), the average age was 1.85 years (ranging from 1- 5 years). This small study shows a comparable bioavailability of oral and intramuscular vitamin K (Konakion MM) administered at high doses in older children with cholestasis. No particular conclusion can be made regarding the effect on K vitamin deficiency bleeding.

CLINICAL STUDY No 4. "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 newborn breast-fed babies"

➢ **Description**

➢ **Methods**

- Objective(s) - Bioavailability and efficacy of orally administered konakion MM
- Study population /Sample size – 25 newborns (14 male, 11 female), full term, healthy, brest-fed
- Treatments – 1.5 mg vitamin K i.m. versus 3 mg vitamin K oral, within 4 hours of birth
- Outcomes/endpoints - vitamin K1 in plasma and Quick value in cord blood, 24 hours and 24 days after administration, SGOT, SGPT, and alkaline phosphatase
- Statistical Methods

Results.

This study shows that healthy new-born babies are born with very low plasma concentrations of vitamin K1, and therefore are at risk of HDN. More than 50 % of the babies had a value of less than 0.05 ng/ml. 27 % had vitamin K1 plasma levels in cord blood of 0.05-0.14 ng/ml and 22 % fell in the group 0.15-0.25 ng/ml. All Quick values in cord blood were below the minimum of the normal range of 70-100 %.

Oral and parenteral administration of KONAKION MM result in equal bioavailability.

The vitamin K1 levels in plasma after 24 days are on the average down to 0.95 ng/ml after i.m. and to 1.08 ng/ml after oral treatment. 30 % of breast fed babies reachs deficiency levels after 24 days.

CLINICAL STUDY No 5. "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."

- **Description**

Twenty-five new-borns (13 females and 12 males) have been treated with vitamin K1 for prophylaxis of haemorrhagic disease. 14 babies received 3 mg vitamin K1 orally and 11 babies 1.5 mg vitamin K1 i.m. (Ro 01-6722/130). The babies investigated were all healthy new-borns and exclusively breast-fed, over a time period of 4 weeks.

- **Results**

The bioavailability - 24 hours after treatment (about 25 hours after birth) the vitamin K1 levels reached 154 ng/ml after i.m. and 105.38 ng/ml after oral administration. These values decreased during the following 4 days to 22 % respectively 56 % of the 24 hours values. 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.

CLINICAL STUDY No 6 "Efficacy and tolerability of KONAKION MM 2 mg vitamin K1 orally versus 1 mg vitamin K1 intramuscularly in newborn, breast-fed babies."

- **Description**

Thirteen babies (7 males and 6 females) have been treated with vitamin K1 for prophylaxis of haemorrhagic disease. 7 babies received 1 mg vitamin K1 i.m. and 6 babies received 2 mg p.o. The babies investigated were all healthy new-borns and exclusively breast-fed over a time period of at least 4 weeks.

- **Results**

Vitamin K1 was administered 1 mg i.m. or 2 mg p.o. within 2 hours after birth. The two application routes and dosages gave equal plasma levels (p(0.05). Prothrombin had significantly increased during the first 24 days. No adverse events had been reported.
The increase of prothrombin values from 24 hours to 24 days was statistically significant.

CLINICAL STUDY No 7. "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."

- **Description**

A randomized clinical trial was conducted to establish the efficacy of oral administration of vitamin K to new-born breast-fed infants against hemorrhagic disease. Two mg of vitamin K1 were given once p.o. after birth. KONAKION MM (2 mg vitamin K1 p.o.) was compared with KONAKION drops (2 mg vitamin K1 p.o.). Vitamin K plasma levels were measured after 24 hours, 4 days and 24 days. PIVKA-II concentrations were measured after 24 hours and 4 days.

- **Results**

At 4 days and 24 days the vitamin K1 plasma levels were statistically significant lower after administration of KONAKION drops than after administration of KONAKION MM. In the groups which had received KONAKION drops highly significant more positive PIVKA-II values were observed than after administration of KONAKON MM. This was the case for PIVKA-II values after 24 hours and 4 days after birth.

CLINICAL STUDY No 8. "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."

- **Description**

Three groups (n=148) of healthy breast-fed infants who had received at random within two hours after birth either 2 mg p.o. KONAKION MM (n1=50) or 2 mg p.o. KONAKION drops (n2=48) or 1 mg i.m. KONAKION ampoules (n3=50) were studied at the age of 2 weeks and 1 month. Comparative bioavailability, efficacy and tolerability of KONAKION i.m., KONAKION MM p.o. and KONAKION drops p.o.
KONAKION ampoules 1 mg i.m.
KONAKION MM 2 mg p.o.
KONAKION drops 2 % 2 mg p.o.

- **Results**

Comparison of vitamin K1 concentration in plasma, Thrombotest results, and PIVKA-II values at 4 weeks showed that KONAKION MM produced statistically significant higher values compared to the former products. The distribution of the Thrombotest values at four weeks after prophylaxis was comparable to those after conventional intramuscular prophylaxis. PIVKA-II disappeared with all products tested after 4 weeks.

CLINICAL STUDY No 9. "Comparative tolerability and efficacy study: vitamin K1 mixed micelles solution versus vitamin K1 solution containing Cremophor EL both administered in a single dose i.m., to babies suffering from chronic cholestasis."

- **Description**

The aim of the study was to compare the tolerability of a single dose of the mixed micelles solution of vitamin K1 in babies (Vit. K MM) by intramuscular injection to that of the Cremophor EL containing solution of vitamin K1 Roche (Vit. K1). 40 infants below 6 months of age, randomized to receive either commercial vitamin K Roche (Vit. K) (20 mg/ml) or mixed micelles vitamin K (Vit. K MM 10 mg/ml).

- **Results**

The local and general tolerability of the new formulation of vitamin K1 is showed. The injection of the MM formulation did not lead to an increase in either the total or the bound bilirubin levels. There were no significant changes in the transaminases, gamma GT or alkaline phosphatase and no changes in the bile acid levels.

CLINICAL STUDY No 10. "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."

- **Description**

A dose of 1 mg vitamin K1 (KONAKION MM) was given i.v. to 28 premature infants. The dose was repeated by 2 mg vitamin K1 p.o. every 4 weeks until the end of the intensive care period. At day 4 and after 4 and 8 weeks plasma samples for vitamin K1 and PIVKA-II determination were taken by vein-puncture. 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.

➢ **Results**

The average level of PIVKA-II in cord-blood 0.32 AU/ml compares well with previous findings in healthy newborns. 52 % of infants had positive PIVKA-II in the cord-blood. 66.6 % of positive PIVKA-II in cord-blood were eliminated at day 4 after administration of 1 mg vitamin K1 i.v. at birth. At 4 weeks 100 % of PIVKA-II were eliminated, demonstrating that i.v. administration of KONAKION MM is an effective and well tolerated prophylaxis of hemorrhagic disease also in premature infants.

CLINICAL STUDY No 11. "Pharmacokinetics of a single dose of vitamin K1 (10 mg) mixed micelles solution administered intramuscularly to 4 cholestatic babies."

➢ **Description**

The plasma evolution of vitamin K1, free and bound bilirubin was investigated after a single dose of KONAKION MM (10 mg) administered intramuscularly to 4 cholestatic babies.

➢ **Results**

The injection of vitamin K mixed micelles solution established a high concentration in the plasma of the patients, peaking at 12 hours with 2174 ng/ml. 96 hours after the injection the plasma concentration decreased to 14 ng/ml. There were no changes in the concentrations of bound bilirubin expressed as percentage of total bilirubin. Glycocholic acid in a relatively large amount (54.6 mg/ml) in the blood has no effect on the ratio of bound bilirubin to total bilirubin.

CLINICAL STUDY No 12. "A comparison of the effect of a single intramuscular injection of Konakion MM pediatric formulation (Ro 01-6722/139) or Konakion Cremophor (castor oil) formulation (Ro 01-6722/119) administered at birth on plasma Vitamin K levels in healthy breast-fed neonates at day 1 and 14 days after birth."

➢ **Description**

➢ **Methods**

- Objective(s) - to compare the effect of a single 1 mg intramuscular injection of Konakion MM pediatric formulation (Ro 01-6722/139) or Konakion Cremophor (castor oil) formulation (Ro 01-6722/119) administered at birth on plasma vitamin K levels in healthy breast fed neonates at day 1 and 14 days after birth.
- Study design - Open, randomized, 2 parallel groups.
- Study population /Sample size - 73 randomized; 40 (20 per treatment) evaluable subjects. Healthy, breast fed, full-term neonates of either gender.
- Treatments – Konakion MM pediatric vs Konakion Cremophor 1 mg i.m.
- Outcomes/endpoints - Vitamin K1 plasma concentrations on day 1 and day 14. PIVKA II concentrations (surrogate marker) on day 1 (cord blood) and day 14.

➢ **Results**

- Efficacy results - both formulations of Konakion provided adequate Vitamin K1 exposure on day 1, and continued exposure at day 14. Higher plasma levels of Vitamin K1 were seen in the Konakion MM group, compared with the Konakion Cremophor group, but the per protocol analysis demonstrated 'non-inferiority' of the Konakion MM formulation. Positive PIVKA IIs decreased from 65% in the Konakion Cremophor group and 60% in the Konakion MM group on day 1 to 5% in the Konakion Cremophor group and 0% in the Konakion MM group on day 14.

- Safety results - Neither formulation was associated with any serious or treatment-related adverse events or safety concern.

CLINICAL STUDY No 14. "A comparison of the effect of oral Vitamin K1 (Ro 01-6722/139) and intramuscular Vitamin K1 (Konakion® Tween 80, Ro 01-6722/143) in exclusively breast-fed neonates on PIVKA II plasma concentrations, Vitamin K1 plasma concentrations and prothrombin time."

- **Description**
- **Methods**
  - Objective(s) - The effect of 2 mg oral doses of Ro 01-6722/139 at birth and at 7 and 30 days after birth were compared to a 1 mg single intramuscular dose of Konakion® at birth on: PIVKA (Protein Induced by Vitamin K Absence) II and Vitamin K1 plasma concentrations plus the International Normalized Ratio (INR) values at 14, 30, and 56 days after birth.
  - Study design - open label, randomized treatment, parallel-group comparison done at two centers.
  - Study population /Sample size – 156 neonates.
  - Treatments - 79 neonates were randomized to the oral and 77 neonates were randomized to the intramuscular formulation.

- **Results**

The PIVKA II response was similar in both treatment groups on days 14 and 30 but differed on day 56. In each group there was one positive PIVKA II value on day 14 and no positive PIVKA II value on day 30. On day 56. there were no positive PIVKA II values in the oral group. However, there were three positive PIVKA II values in the i.m. group. The plasma Vitamin K1 concentration (ng/ml) was larger on day 14 for the oral treatment group (X ± SD: p.o., 2.0 ± 1.6 vs i.m., 1.3 ± 1.1: P= 0.007) and similar on day 30 (p.o., 0.5 ± 0.3 vs im. 0.5 ± 0.7: P = 0.11). On day 56 the vitamin K1 concentration was higher in the oral formulation group than in the i.m. formulation group (P = 0.003). The INR was similar in both treatment groups on days 14, 30, and 56. There was no adverse event related to a deficiency in the clotting mechanism or an elevated INR value that warranted the discontinuation of treatment. The number of subjects having an adverse event and the total number of adverse events were similar in both treatment groups. The adverse events were categorized primarily as mild and unrelated to treatment.

CLINICAL STUDY No 15. "Plasma vitamin K1 and PIVKA - II levels in breast fed infants after repeated oral administration of Ro 01-6722/141 (2 x 0.25 mg vitamin K1)".

- **Description**
- **Methods**
  - Objective(s) - To test the hypothesis that lower oral dosages (0.25 mg) and more frequent administration of Konakion MM results in adequate plasma vitamin K1 and PIVKAs to protect babies from late haemorrhagic disease of the newborn.
  - Study design - Open controlled study
  - Study population /Sample size - 46 newborn breast-fed infants
  - Treatments - p.o.1st Dose: 0.25 mg vitamin K1
    la) 0-4 hours 0.125 mg
    2b) 4 h-1 day, 0.125 mg
    2nd Dose: 0.25 mg vitamin K1 at Guthrie-Test, 6-10 days after birth

3rd Dose: In the 4th week, after blood sampling, 0.25 mg vitamin K1 and another 0.25 mg every 4 weeks until the infant was receiving less than 50% of its intake from breastfeeding

- Outcomes/endpoints - Vitamin K1, PIVKA-II. Bilirubin conjugated and total. Adverse events monitored.

➢ **Results**

- Efficacy results - Vitamin K1 given as Konakion® MM paediatric in two small doses (0.125mg) on the first day of life and 0.250 mg on the 5th or 6th day after birth resulted in average vitamin K1 levels of 0.76 ng/ml with a variability of over 80%.

Multiple, low dose administration of Vitamin K1 does not represent significant progress in the search for a safe and effective prophylaxis of haemorrhagic disease in newborns. Results revealed variable plasma levels in the 4th week (>80%), similar to plasma levels in four week old unsupplemented infants or to plasma levels in four week old infants after a single dose of vitamin K1 at birth.

The vitamin K1 levels found during this study were not completely reliable because about 22% of the infants had already been fed baby formula in addition to breast milk.

CLINICAL STUDY No 16. "Plasma levels of vitamin K1 and PIVKA levels in breast fed infants after repeated oral administration of 0.5 mg vitamin K1".

➢ **Description**

➢ **Methods**

- Objective(s) - To test the hypothesis that lower oral dosages (0.5 mg) and more frequent administration of Konakion® MM produce adequate plasma levels and PIVKAs to protect newbom babies from late haemorrhagic disease.
- Study design - Open controlled study
- Study population /Sample size - 50 newborn breast-fed infants
- Treatments – oral 0.5 mg vitamin K1 (Konakion MM)

1st dose: 0-4 hours after birth
2nd dose: 2-4 days after birth
3rd dose: 10-15 days after birth
4th dose: 30 days after birth

➢ **Results**

- Efficacy results - The administration of repeated oral doses of vitamin K1 (0.5 mg at birth, 0.5 mg 2-4 days, 0.5 mg 10-15 days) cannot be considered an effective prophylaxis of haemorrhagic disease in neonates. Plasma levels of PIVKA-II and vitamin K1 are comparable to levels in unsupplemented infants.

CLINICAL STUDY No 17. "Plasma vitamin K1 and PIVKA-II levels in breast fed infants after oral administration of Ro 01-6722/141(0.25 mg vitamin K1) at birth."

➢ **Description**

➢ **Methods**

- Objective(s) - Dose range finding for oral administration of Konakion MM (Ro 01-6722/141) after 0.25 mg vitamin K1 after birth.
- Study design - Open controlled study

- Study population /Sample size – 51 Healthy breast-fed newborns.
- Treatments - p.o.0.25 mg vitamin K1:
  1st dose: 1a) 0-4 hours 0.125 mg
  1b) 4h - 1 day 0.125 mg
  2nd dose: at Guthrie-Test, 6-10 days after birth to all breast-fed babies 0.50 mg vitamin K1
  3rd dose: in the 4th week, 0.50 mg vitamin K1 and for breast-feeding women after 4 weeks every 4 weeks until the end of breast feeding.

➢ **Results**

- Efficacy results - 51 PIVKA's and 49 vitamin K1 plasma levels were determined. The average plasma levels after 6 days (6.54 ± 0.85 days) was 1.24 ± 1.13 ng/ml (median 0.85 ng/ml). Three out of 51 PIVKA's were positive. It is concluded that when comparing these results with the results from previous studies and results of bottle-fed infants the low dose supplementation is ineffective and can therefore not be recommended.

Discussion on clinical aspects
As MAH states, the term "bioavailability study" for several of these studies is misleading since different doses for the two formulations were used and only one plasma sample per patient was taken. Therefore it is impossible to calculate any of the standard bioavailability parameters. Even though a bioavailability in the strict sense was not determined in the trials listed it could be demonstrated that the MM formulation was able to generate systemic vitamin K concentrations using oral doses similar to an i.m. injection.
No new safety signals were detected.

CLINICAL STUDY No 18. "Intracerebral Hemorrhage due to Hemorrhagic Disease of the Newborn and Failure to Administer Vitamin K at Birth"

➢ **Description**

➢ **Methods and results**

- Study design – case report
- Study population /Sample size – two 5 week-old healthy infants, who had not received vitamin K prophylaxis, both presented with intracranial hemorrhage, prolonged PT, PTT. Treatment included rFVIIa, fresh frozen plasma, red blood cell transfusion. One of infants was left with severe neurological complication, poor swallow function.

Discussion on clinical aspects
This case report also confirms that late VKDB frequently manifests as intracranial hemorrhage. No safety signals were detected in this case report.

CLINICAL STUDY No 19. "Neonatal vitamin K prophylaxis in Great Britain and Ireland: the impact of perceived risk and product licensing on effectiveness"

➢ **Description**

➢ **Methods**

- Objective(s) – to determine current use of vitamin K (VK) prophylaxis in newborns and review the efficacy and effectiveness of regimens used.

- Study design - Efficacy and effectiveness calculated using current practice details, data from Southern Ireland and two previous surveys, together with contemporaneous studies of vitamin K deficiency bleeding (VKDB).
- Study population /Sample size
- Outcomes/endpoints - Current VK prophylaxis following uncomplicated term deliveries. Relative risk of VKDB calculated for the VK actually received and for ‘‘intention to treat’’.

Results

- Efficacy results - Questionnaire response rate 95% (n = 243), all recommending VK prophylaxis. No association between unit size and route of administration. For uncomplicated term deliveries, 60% recommended intramuscular (IM) prophylaxis, 24% oral and 16% offered both routes without bias. All units offering IM gave a single dose, mostly 1 mg Konakion Neonatal. Oral regimens showed more variation: two thirds gave 2 mg (range 0.5–2 mg), the number of doses ranged from 1 to 11 and many used preparations off-licence or the unlicensed Orakay. IM prophylaxis, if given, provided the best protection (most efficacious) against VKDB. However, on an intention-to-treat basis (effectiveness), there is no statistically significant difference between the risks of VKDB after intended IM vitamin K and after oral prophylaxis intended to continue beyond a week.

CLINICAL STUDY No 20. “Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993–94 and 2001–02”

- **Description**
- **Methods**
  - Objective(s) - To conduct and report monitoring of vitamin K deficiency bleeding (VKDB) in Great Britain and Ireland following the 1988–90 survey (VKDB-90).
  - Study design - Two 2-year surveys conducted during 1993–4 (VKDB-94) and 2001–02 (VKDB-02).
  - Study population /Sample size - All infants presenting with bleeding resulting from vitamin K deficiency
  - Outcomes/endpoints - Incidence of VKDB, related mortality/morbidity and VK prophylaxis recommended/received, noting predisposing features.

Results

- Efficacy results - Compared with previous studies, VKDB-02 found fewer cases of VKDB (RR: 0.27 (95% CI: 0.12 to 0.59), p,0.001) with no deaths, no long-term morbidity and reduced incidence among those receiving any oral dosing (RR: 0.24 (95% CI: 0.06 to 1.01), p,0.059). Breast-fed infants accounted for the vast majority of cases. The number receiving no prophylaxis fell consecutively over time: 20 of 27 in VKDB-90, 10 of 32 in VKDB-94 and 4 (because of parental refusal) of 7 in VKDB-02. Seven received one oral dose of VK in VKDB- 90, 16 in VKDB-94 and none in VKDB-02. Underlying liver disease was found in six cases in VKDB-90, 12 in VKDB-94 and one in VKDB-02.: In the most recent survey, the incidence of VKDB was about one third that in the two earlier studies. Late onset VKDB remains virtually confined to breast-fed infants who have received either no vitamin K or just one oral dose. The effectiveness of oral prophylaxis regimens has improved over the last 15 years, but parental refusal of prophylaxis has become more problematic.

CLINICAL STUDY No 21. "Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries"

- **Description**
- **Methods**
  - Objective(s) - to compare the risk of vitamin K deficiency bleeding under different propylactic regimens in infants with biliary atresia. Newborns routinely receive vitamin K to prevent vitamin K deficiency bleeding. The efficacy of oral vitamin K administration may be compromised in infants with unrecognized cholestasis.
  - Study design – retrospective cohort study, infants from Dutch and Danish national biliary atresia registries, who were either breastfed and received 1 mg of oral vitamin K at birth followed by 25 µg of daily oral vitamin K prophylaxis (Netherlands, 1991– 2003), 2 mg of oral vitamin K at birth followed by 1 mg of weekly oral prophylaxis (Denmark, 1994 to May 2000), or 2 mg of intramuscular prophylaxis at birth (Denmark, June 2000–2005) or were fed by formula. The absolute and relative risk of severe vitamin K deficiency and vitamin K deficiency bleeding on diagnosis in breastfed infants on each prophylactic regimen and in formula-fed infants was determined.
  - Study population /Sample size – 185 patients from Dutch and Danish biliary atresia registry, 140 cases analyzed.

- **Results**
  - Recruitment/ Number analysed – 145 patients
  - Efficacy results - Vitamin K deficiency bleeding was noted in 25 of 30 of breastfed infants on 25 µg of daily oral prophylaxis, in 1 of 13 on 1 mg of weekly oral prophylaxis, in 1 of 10 receiving 2 mg of intramuscular prophylaxis at birth, and in 1 of 98 formula-fed infants (P= 0.001). The relative risk of a bleeding in breastfed compared with formula-fed infants was 77.5 for 25 µg of daily oral prophylaxis, 7.2 for 1 mg of weekly oral prophylaxis, and 9.3 for 2 mg of intramuscular prophylaxis at birth.

Discussion on clinical aspects
A daily dose of 25 µg of vitamin K failed to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. One milligram of weekly oral prophylaxis showed higher protection to these infants and is of similar efficacy as 2 mg of intramuscular prophylaxis at birth.

CLINICAL STUDY No 22. "Late haemorrhagic disease of the newborn"

- **Description**
- **Methods**
  - Objective(s) – to describe and analyze cases of hemorrhagic disease of the newborn in Kocaeli within 3 year period.
  - Study design – retrospective analysis.
  - Study population /Sample size – hospital records for 4916 children hospitalized between February 2002 and April 2005 in the tertiary centre in Kocaeli, eight infants with nine episodes of late hemorrhagic disease of the newborn.
  - Treatments – prophylaxis with intramuscular vitamin K in one case, no further information.

- **Results**
  - Recruitment/ Number analysed – 4916 patients hospitalized, 9 cases of late VKDB

- Baseline data - The median age at presentation was 46 (26–111) days. All the infants were born at full-term and were exclusively breast-fed. All had an uneventful perinatal history, except one who had meconium aspiration. One patient had received intramuscular vitamin K at birth, four patients had received no vitamin K prophylaxis and another three had uncertain histories. At presentation, six had intracranial bleeding and the remainder had bleeding either from the venipuncture site or the gastro-intestinal tract. The presenting signs and symptoms were irritability, vomiting, bulging or full fontanelle, convulsions and diminished or absent neonatal reflexes. Galactosaemia was detected in a 2-month-old infant with prolonged jaundice. There was no surgery-related mortality or complications but one survived for only 2 days on ventilatory support following surgery. One of the six survivors had severe neurological sequelae.

Discussion on clinical aspects
No new particular safety issues were detected.

CLINICAL STUDY No 23. " **INTRACRANIAL HEMORRHAGE DUE TO LATE HEMORRHAGIC DISEASE IN TWO SIBLINGS"**

- **Description**
- **Methods and results**
  - Study design - case report
  - Study population /Sample size – 2 cases.
  - Case 1 – 43 day old girl, full term, exclusively breastfed, no prophylaxis with vitamin K at birth. Presented with left subdural haemorrhage. Treatment with 3 mg vitamin K (route not specified), red blood cell transusion, intravenous vitamin K, aspiration of hematoma. The baby died 54 h after admission.
  - Case 2 – 45 day old boy, breastfed, no prophylaxis with vitamin K at birth, presented with hemorrhage in ventricles. Treatment included 3 mg of vitamin K intravenously, red blood cell transusion. PT and PTT improved within 18 hours after administration.

Discussion on clinical aspects
This case report confirms the seriousness of late VKDB in infants, as it resulted in intracerebral hemorrhage and one death. Treatment with vitamin K and supportive measures were not sucessful in one case and resulted in death.

CLINICAL STUDY No 24. "Serious and life-threatening bleeding in late vitamin K deficiency"

- **Description**
- **Methods**
  - Study design - a retrospective analysis of 12 cases.
  - Study population /Sample size – 12 patients (aged 22 days – 18 months) within 4 month period in India.
  - Patients were full term, none has received vitamin K prophylaxis. Three cases had a history of diarrhoea and had received oral antibiotics. Treatment included vitamin K 5 mg intravenously and fresh frozen plasma, if necessary.

Discussion on clinical aspects

This is a short report containing limited information. Some cases do not conform to the classical definition of VKDB. It shows, however, an increased risk of VKDB in patients with diarrhea and administration of antibiotics (not specified). No new efficacy or safety information was provided.

CLINICAL STUDY No 25. "Intracranial hemorrhages due to late-type vitamin K deficiency bleeding"

- **Description**
- **Methods**
  - Study design – case report
  - Study population /Sample size - Data of 12 infants treated for intracranial hemorrhage due to late-type VKDB in Baskent University Hospitals between June 1998 and June 2005 have been analyzed.

- **Results**
  - Baseline data – The ages of patients ranged between 25 and 90 days. All were breast-fed except one who was fed also with formula. Five were born in the hospital and seven were born at home. None of the infants born at home received vitamin K prophylaxis. Hemorrhages were classified as intraparenchymal in 58.33%, subarachnoid in 50.00%, subdural in 50.00%, intraventricular in 41.66%, and epidural in 8.33% according to cranial computerized tomography findings. Surgery was performed in seven cases (58.33%). A total of six patients died (50.00%). Three of the deaths were from the surgery-performed group.
  - Efficacy results - Intravenous vitamin K of 3 mg was administered to all patients, and PAT and PTT showed improvement within 4-6 hours.
    Intramuscular vitamin K prophylaxis was administered in 2 children born at the hospital, but there is no reliable history in the other 3 infants. VKDB was observed secondary to cholestasis in two patients, and 10 cases were primary VKDB.

Discussion on clinical aspects
Only two of the infants have undoubtedly received vitamin K prophylaxis, but it suggests that single-dose intramuscular prophylaxis may not be sufficient. Treatment with 3 mg intravenous vitamin K was effective in reversing VKDB.

CLINICAL STUDY No 26. "Vitamin K deficiency bleeding presenting as impending brain herniation"

- **Description**
- **Methods and results**
  - Study design – case report
  - Two month old boy, exclusively breast-fed, no information regarding vitamin K prophylaxis was provided. Bilateral subdural haemorrhage was diagnosed by CT scan. Vitamin K (dose not specified), fresh frozen plasma and packed red blood cell transfusion was given, PT, APTT and INR improved.

Discussion on clinical aspects
No firm conclusions can be made from this case report, as important information is lacking (information on prophylaxis and the dose of vitamin K for treatment).

CLINICAL STUDY No 27. "Life-threatening retroperitoneal hemorrhage due to late vitamin K deficiency"

- **Description**
- **Methods and results**
  - Study design – Case report
  - 31 day old boy, full term, no vitamin K prophylaxis, exclusively breast-fed, presented with right retroperitoneal hemorrhage. Liver function tests were normal. He was treated with intravenous vitamin K (1 mg/kg vitamin K1, 20 mg/2 ml, Liba, Turkey), fresh plasma and red blood cell transfusions. PT and aPTT returned to normal values in six hours following the administration of i/v vitamin K.

Discussion on clinical aspects
This study presents a rare bleeding localization in a healthy newborn. VKDB was sucessfuly reversed by intravenous vitamin K 1 mg/kg administration. No side-effects and no other safety signals were detected.

CLINICAL STUDY No 28. "Delayed vitamin K deficiency as a cause of bleeding: still a concern in the 21st century!"

- **Description**
- **Methods and results**
  - Study design – a retrospective analysis of 11 case reports in single tertiary care centre in India.
  - Study population - patients aged 2 – 16 months.
  - Results: two patients presented with intracerebral haemorrhage, others with extensive bruise, haematoma, bleeding or epistaxis. These patients had significant co-morbidities – one patient had tuberculosis and was receiving antituberculosis drugs for 1 month prior (not specified), 4 patients had diarrhoea, all had fever. The type of vitamin K prophylaxis is not specified.

Discussion on clinical aspects
This case report contains limited information, as the type and dose of K vitamin prophylaxis is not specified, furthermore most of these cases can not be attributed to classical definition of VKDB, because patients were older than 6 months and had significant comorbidities, fever.

CLINICAL STUDY No 29. "Intracerebral hemorrhage despite prophylactic administration of vitamin K in infants"

- **Description**
- **Methods and results**
  - Study design – case report from Japan.
  - Study population /Sample size – 2 cases.
  - Case one - 48-day-old boy presented with intracerebral hemorrhage (late onset VKDB). He had received oral prophylaxis with vitamin K 2 mg on the day of birth, at ages 5 days and 1 month. Breast-fed.
  - Case 2 - 60-day-old boy presented with intracerebral hemorrhage (late onset VKDB). He had received oral prophylaxis with vitamin K 2 mg on the day of birth, at ages 5 days and 31 days. Breast-fed.

Both infants had liver dysfunction, as evidenced by blood tests.

Discussion on clinical aspects
This case report describes the failure of oral prophylaxis using 2 mg x 3 regimen, although the authors conclude that the overall incidence of early and classic VKDB in Japan has decreased markedly, late VKDB still occurs. No new safety signals were detected, as liver dysfunction has been described as a risk factor in oral prophylaxis.

➢ Rapporteur's overall conclusion after assessment of initial submission

The submitted studies provide useful data regarding dose recommendations, pharmacodynamic, pharmacokinetic and safety information in paediatric population, but additional specific information regarding dose recommendations and safety should be provided.

List of questions:

- MAHs are invited to provide further information on phytomenadione safety aspects regarding reported association of i.m. vitamin K and childhood leukemia, as this issue has not been covered in the submitted studies.

- MAHs are also invited to provide information on studies concerning vitamin K dosage in treatment of children with haemorrhage.

Assessment of Applicant's RESPONSE:

Following circulation of preliminary Assessment Report additional questions have been raised by other Member States. Generally Rapporteur's position was endorsed and a summary of Applicant's response to specific questions is provided below:

- *Member State Comment*

Specific comments
The Rapporteur noted that vitamin K is also licensed for the treatment of overdose with coumarin anticoagulants in children. We would therefore like to request the MAHs to provide all available evidence on the use and posology of vitamin K dosage in reversal of coumarin anticoagulation with the intention to propose the inclusion of this indication in SmPCs across EU.

- *Member State Comment*

There is no consensus between European countries regarding prophylaxis in exclusively breast-fed infants to prevent haemorrhagic disease of the newborn.
Indeed, in this indication, there are possibly two routes of administration, parenteral (i.m. or i.v.) or oral administration, and several dosing regimens according to countries. As an example, dosing regimens that can be recommended for oral route are: doses of 2 or 1 mg, treatments

limited to 3 doses or weekly administered up to 3 months or more, or lower daily doses administered during 3 months.
It is not well understood whether a consensus for dosing regimen is sought throughout this worksharing Article 45 paediatric, since no clear wording for the SmPC (notably section 4.2) is proposed by the MAH, We are of the opinion that dose recommendations should be further assessed before any final wording is endorsed and therefore we endorse the Rapporteur's conclusion that additional information regarding dose recommendations should be provided by the MAH.
The MAH should notably provide justifications regarding the choice of the doses (whether 2 or 1 mg) and the duration of treatment (whether a 3 dose regimen or a prolonged treatment up to 3 months or more). Furthermore, SmPC wording should be proposed accordingly, notably for sections 4.1 and 4.2.

We have currently some reports of dosing errors, more precisely parents having administered daily doses of vitamine K1 instead of weekly doses. This represents a risk of overdose. Fortunately, no adverse events or only a few cases considered as medically not relevant have been reported.
Several measures have been taken:
- amendment of the patient leaflet in order to improve the comprehension of the posology by parents,
- addition of a warning for exclusively breast-fed infants on the packaging,
- communication to health care professionals regarding correct drug utilisation.
However, we are still receiving reports of dosing errors.
We would be interested to know whether such issue exists or not in other European countries and how they handle this unusual mode of administration.
Also, it would be interesting to compare the different packagings available in Europe.

Applicant's response (Roche):

QUESTION 1: association with childhood leukemia
When administered to children, usually newborns, Vitamin K is intended as a prophylactic single dose against Vitamin K deficiency bleeding (VKDB). The choice of administration of Vitamin K for neonatal prophylaxis in newborns includes both oral and intramuscular (IM) routes. Amongst the prophylactic strategies used in the neonatal period, research has considered IM prophylaxis (dose of 1.0 milligram) as a favourable option because of the ease of administering a single injection, its ability to correct the deficiency and because the route provides almost full protection from both early and late VKDB**.** Furthermore, in 1993, a task force of the American Academy of Pediatrics (AAP) recommended that Vitamin K should be administered to all newborn children via the IM route.

A thorough literature search, an epidemiological review and a search of the Roche safety database provided no evidence of an association between the administration of IM Vitamin K and the subsequent development of childhood leukaemia. The literature search revealed that all relevant studies published were unable to confirm a link between IM Vitamin K and childhood leukaemia as suspected by Golding *et al*. The epidemiological review supports the findings of the literature review. There were also no childhood leukaemia related cases retrieved from the Roche safety database. It is of note regarding the epidemiological review, that the MHRA commented during the assessment (*Day89_PdAR_Phytomenadion_30_03_2012*) of the initial submission for this procedure that:

"An Expert Working Group was then formed to review all the available studies and the Group considered that the evidence suggested that there was no increased risk of solid tumour in

association with vitamin K and that there was no basis for recommending a change to the current licensing position of Konakion." In conclusion the totality of the available evidence does not alter the benefit-risk ratio of using IM Vitamin K. No change to the product label is warranted.

A thorough literature search was conducted by the Roche Data Management Group on 16 March 2012 in several databases (Medline, EmBase and Derwent Drug File) for 'Vitamin K', 'Konakion' and 'leukemia in children'.

The literature search returned 105 papers, of which 12 papers contained original relevant data (Table 1).
The first studies initiated to investigate the proposed relationship between Vitamin K and leukemia took place in Sweden, the USA, Denmark, the UK, and Germany. No evidence was found to support this hypothesized relationship in any of these studies, based on the authors' interpretation of the data.
There were however methodological issues with these studies, which included a lack of statistical power, presumed rather than documented exposure to Vitamin K, a lack of hospital-matched controls and inputting missing data. In an attempt to address some of these issues, McKinney et al. conducted a well-designed case control study on a large population broken down into leukaemia subtypes, and Parker et al.used hospital-matched controls. No link between Vitamin K and leukemia could be found in either of these studies, strengthening the findings of the previous studies.
The most recent study retrieved is also the most comprehensive ever undertaken on this topic. In a national (UK) casecontrol study of 2,530 children with cancer (of whom 1,174 had leukemia), no convincing evidence was found that Vitamin K administration causes leukaemia or any other cancer, irrespective of the posology. The authors reached the same conclusion when presenting an overview of all the studies to this point in time.

Table 1 : Overview of the twelve relevant studies from the literature Search

References (chronological order)	**Patients (n)**	**Design**	**Outcome reported**
Ekelund et al. 1993 Sweden	396 (cancer) 200 (controls)	Modified case-control (IM VK vs. oral VK)	Association between Vitamin K and all cancers/leukemia could not be verified
Klebanoff et al. 1993 USA	48 (cancer) from 54,795 births	Nested case-control	No association between Vitamin K and any childhood cancer/leukemia
Olsen et al. 1994 Denmark	586,378 (children who received Vitamin K)	Cohort study (IM VK vs. maternal VK vs. no VK)	No trend in risk of childhood cancer or leukemia from Vitamin K
Ansell et al. 1996 UK	109 (leukemia) 218 (controls)	Case-control (IM VK vs. oral VK + no VK + no record)	Findings do not support suggestion VK linked to leukemia
von Kries et al 1996 Germany	272 (cancer) 334 (controls)	Case-control (IM + i.p. VK vs. oral + no VK)	Association between Vitamin K and cancer or leukemia could not be confirmed

Kaatsch et al. 1996 Germany	425 (cancer) 610 (controls)	Case-control (IM + i.p. VK vs. oral + no VK)	Association between Vitamin K and cancer or leukemia could not be confirmed
Roman et al. 1997 UK	177 (cancer) 368 (controls)	Case-control	No relationship between leukemia and Vitamin K noted
McKinney et al. 1998 UK	150 (leukemia) 46 (lymphomas) 79 (CNS tumors) 129 (acute lymphoblastic leukemia) 777 (controls)	Case-control (IM vs. oral VK; IM vs. no VK; oral VK vs. no VK)	Increased risk of leukemia from Vitamin K is not confirmed
Parker et al. 1998 UK	664 (cancer)	Case-control (IM vs. no VK)	No evidence of relationship between Vitamin K and cancer
Passmore et al. 1998 UK	597 (cases) 597 (controls)	Case-control (IM VK, cancer vs. no cancer)	Cannot exclude possible relationship between Vitamin K and cancer or leukemia
Roman et al. 2002 UK/Germany		pooled analysis of studies [8, 10-12, 14, 15, 17] (IM VK vs. control)	No convincing evidence of relationship between Vitamin K and leukemia

A prospective case-control study conducted in the United Kingdom (UK) collected information on 16,193 newborn children (< or =7 days of age) and later identified those who developed cancer (n=33) within 10 years of life by 1980. These 33 children were compared with 99 controls (three for each case). Of these, 16 cases and 27 controls received Vitamin K. A smaller number of cases and controls received other drugs. The study found that drug administration, including Vitamin K, to the neonate was a risk factor associated with cancer in childhood, with an odds ratio (OR) of 2.85 (95% confidence interval (CI) 1.16- 6.98). The study reported an unexpected association between childhood cancer and Vitamin K, as this association was contradictory to prior hypotheses.

Another UK study researched infants born in two Bristol maternity hospitals between 1965 and 1987. In the neonatal stage, the infants received IM Vitamin K (n=206) and were compared to controls (n=558). The OR of cancer diagnosed between 1971 and 1991 in the presence of administration of Vitamin K was assessed. The study found a statistically significantly increased risk of cancer for those given IM Vitamin K (OR 1.97, 95% CI 1.3-3.0, p=0.002) compared with those given oral or no Vitamin K. This 1992 study reported that the only two studies thus far that assessed the link between childhood cancer and IM Vitamin K, although with different methodologies, had produced similar results.

From the 10 case-control studies conducted between 1993 and 2003, AAP, in a revised statement, disregarded any causal link between parenteral Vitamin K and cancer in children. It further advocated the use of Vitamin K to prevent early and late VKDB.

A nested case-control study from the United States of America (USA) assessed the link between Vitamin K and cancer in members of the Collaborative Perinatal Project (CPP). Of the children born between 1959 and 1966 (n=54,795) there were 48 cases of cancer. Fourteen subjects received Vitamin K through the IM route, although the results did not specify the cancerous affects in this group alone. The study matched each case child to five randomly selected controls. Sixty-eight percent of 44 case children and 71% or 226 controls received Vitamin K. The OR was 0.47 (95% CI 0.14-1.55) for leukaemia 1.08 (95% CI 0.45-2.61) for other cancers. The study did not find any link between Vitamin exposure and an elevated risk of any or all childhood cancers combined hence proved the safety of IM Vitamin K. Strengths of the study included prospective data collection and a sample which was unlikely to have been biased to cancer in any way. It was also unlikely that the outcome influenced Vitamin K records; the records were more complete than medical data that were routinely collected (as they formed a part of a research study). In addition, the study gathered individual exposure data for nearly 94% of the subjects. Furthermore, the study compared its results to the national data on incidence by age, sex and race which indicated that cancer and leukaemia probabilities at 7 ½ years of age in a cohort identical to the racial characteristics of the CPPP sample were 1.1 and 0.35 per 1,000 respectively. The study findings were identical at incidence rates of 1.1 and 0.4 per 1,000 respectively. This observation indicated that only a few cases, if at all, were not taken into consideration. It was also suggested that it was unlikely to find differences in the probability of cancer detection as case children and controls were matched for the length of the follow-up. The study's weakness was that since controls and case children were not matched by date of birth or study centre, a carcinogen present in one hospital or at any time could artificially strengthen or weaken the link between cancer and Vitamin K, if the latter was being given or not, respectively.

A study examined the association between childhood cancer and IM Vitamin K administration to l,384,424 newborns born between 1973 and 1989. Participants were divided into an IM Vitamin K group (n=1,085,654) and an oral Vitamin K group (n=272,080). There was no increased risk of cancer in the IM group (OR 1.01, 95% CI 0.88-1.17 for all childhood cancers and 0.90, 95% CI 0.70-1.16 for childhood leukaemia). The study could not verify the association it set out to investigate and its conclusions were different from the two studies by Golding et al., quoted earlier in this report, in that this study asserts that IM Vitamin K does not carry a substantial risk for development of childhood cancer. Both Golding's studies and this study had the same preparation and dosage of Vitamin K. The differences may be attributed to the differences in the study populations or designs.

A study compared cumulative cancer risk in Danish infants who were administered IM Vitamin K with the risk of infants who had never received any Vitamin K and with infants whose mothers were administered Vitamin K while pregnant. In Denmark newborns or mothers were not given Vitamin K before 1955. The cohort, in this study, therefore included infants born between 1960 and 1969 and whose mothers were administered Vitamin K while pregnant (n=797,472). The study assumed that almost all children born in the country received IM Vitamin K as they were largely hospital births since the 1970s and the use of Vitamin K was relatively common by then. The IM Vitamin K-receiving cohort was therefore the one born between 1975 and 1984 (n=586,378). The relative risk (RR) (i.e., ratio between cumulative risks at 13 years of age) of cancer (IM versus no Vitamin K) was 1.00 (95% CI 0.93-1.09) for leukaemia and RR of 1.15 (0.97-1.36) for malignant lymphomas and 1.29 (1.23-1.35) for all tumour types. The study found that common use of IM Vitamin K since the 1970s affected the trend in childhood cancer risk, particularly for leukaemia and that the results of this study did not match that of Golding et al. (1992) cited earlier in this report.

A population-based case-control study of children born between 1975 and 1993 in Germany, examined the possible association between parenteral Vitamin K prophylaxis and cancer in childhood. There were 272 children with leukaemia, nephroblastoma, rhabdomyosarcoma, neuroblastoma and tumours of the central nervous system who were diagnosed between July 1988 and June 1993 and were aged between 30 days and 15 years at diagnosis. There were 334 population-based controls without cancer diagnoses. Parenteral Vitamin K was given in 176 cases including IM (n=147) and subcutaneous (n=28) and to 205 controls including IM (n=174) and subcutaneous (n=30). The study did not confirm a causal link (unlike the study of Golding et al. 1992) between parenteral Vitamin K exposure and cancers in childhood including leukaemia and other tumours combined, i.e., OR of 1.04, 95% CI 0.74-1.48). The observed leukaemias had an OR of 0.98 (0.64-1.50). When leukaemia cases were compared with local controls OR was 1.24 (0.68-2.25) and OR of state controls was 0.82 (0.50-1.36). The differences in results between this study and Golding et al. were attributed to varied study design. Von Kries et al. overcame the design flaws observed in the study by Golding et al. They matched controls for age and sex, instead of unmatched controls which Golding et al. used. Also, unlike Golding et al., this study was population-based. Von Kies et al. also claimed that they considered data that was more accurate and complete regarding whether Vitamin K was ever given.

A case-control study from the UK presented findings relating to the association between prenatal and neonatal exposures of Vitamin K and leukaemia. The study included children aged zero to 14 years with leukaemia and two controls per case, matched for hospital, sex, year and month of birth. Two types of findings were reported including reference to mothers' obstetric notes and by what was imputed from policy of the hospital. Adjusted OR for those with acute lymphoblastic leukaemia (ALL) and given IM Vitamin K, i.e., 72 cases and 142 controls (according to medical obstetric or neonatal notes) was 1.0 (95% CI 0.5- 1.9) whereas for all leukaemia diagnosis and given IM Vitamin K, i.e., 86 cases and 163 controls the OR was 1.2 (0.7-2.3). For those with ALL and with IM Vitamin K status imputed from hospital policy, i.e., 85 cases and 171 controls, the OR was 0.8 (0.3-2.0). For all leukaemia diagnosis and with IM Vitamin K status imputed from hospital policy, i.e., 100 cases and 196 controls, the OR was 1.1 (0.5-2.6). Regardless of the method used to present the data, the study’s findings do not corroborate that the risk of leukaemia in children is elevated amongst neonates who were given IM Vitamin K.

A population-based case-control study was conducted with data from hospital records on children resident in Scotland (age range 0-14 years). Between 1991 and 1994, they were diagnosed with leukaemia (n=150), lymphomas (n=46), central nervous system tumours (n=79), other solid tumours (n=142) and a subset of ALL (n=129). They were matched with 777 controls by sex and age including 417 matched sets (n=360 triplets, n=57 pairs), to analyze the data. In all 1,194 case and control cases note abstractions and matched sets by diagnostic group were analyzed. For the records/note abstractions, the adjusted ORs for IM Vitamin K administered in the neonatal stage were 1.23 (0.77-1.97) for the leukaemia diagnostic group, 1.17 (0.70-1.97) for the ALL group, 1.70 (0.59-4.95) for the lymphomas group, 1.07 (0.55-2.09) for the central nervous system tumours group, and 0.60 (0.36-1.03) for the other solid tumours group. This study did not support the earlier observations of an increased risk of childhood cancer and leukaemia linked to administration of Vitamin K through the IM route. The strength of this study was that it circumvented the conventional problem of maternal recall bias linked with interview-based studies, because it extracted independent data for various variables, comprising neonatal Vitamin K prophylaxis from medical notes. Besides, cases in this study greatly represented the population and the number of cases analyzed was also higher than those in prior similar studies. This was also the only study that documented risks for individual groups of childhood solid tumours, in particular brain tumours. This study recognized that individual diagnostic groups of childhood cancer may have different aetiologies; hence the study investigated the most biologically plausible subsets. The study also presents new results for childhood central nervous

system tumours. Investigators used a structured and validated recording form which facilitated systematic data recording and reduced the possibility of bias introduction into the abstraction procedure. Lastly, this study had 89% power to identify an OR of 1.5 at 5% level of significance, where two controls per case were assumed and a 60% prevalence of IM Vitamin K exposure, which is consistent with other studies, such as that of Von Kries et al..
An ecological study was conducted to compare the incidence of cancer in children's groups classified by the policy on Vitamin K at the hospital in which they were born between 1966 and 1991 (n=3.7 million births) in England, Scotland, and Wales. The objective was to establish the association, if any, between development of childhood cancer before the age of 15 years and neonatal administration of IM Vitamin K. The study identified 3,266 childhood cancers amongst all births. The 94 hospitals had varying Vitamin K policies. The study compared rates of malignant disease post-births in hospitals whose policy on use of IM Vitamin K was either consistently non-selective or consistently selective or sometimes non-selective and sometimes selective. The study also presented risk ratios to compare non-selective and selective policy of all hospitals together. These risk ratios (an estimate of ratio of average risk of stated disease for group of children born in hospitals with non-selective policy versus that for children born in hospitals with selective policy) ranged between 0.94 and 1.14. The study's mainly negative results were consistent with results of other studies in this area and the overall results were insignificant.

A case-control study in England and Wales examined the possible association between neonatal administration of IM Vitamin K and cancer in childhood.
Subjects were 597 children (cases) born between 1968 and 1985 and diagnosed with malignant tumours between 1969 and 1986 and controls were matched for month and hospital of birth and sex. The study found a borderline significant association between all cancers and IM Vitamin K with OR of 1.44 (1.00-2.08), p=0.05. The association with leukaemia was the strongest at 1.53 (p=0.17). This study therefore, proved an association between neonatal administration of IM Vitamin K and cancer in childhood; however the study attributes this finding to abnormal deliveries. Since this study's results were inconsistent with findings of other previous studies which found no causal association, the study concluded that any potential risk was possibly quite small.

A retrospective case-control study based on hospital birth records was conducted in the former Northern Health region of England. Subjects included children (n=685) born in the region between 1960 and 1991 and who developed cancer before 15 years of age. There were 3,442 controls matched for date and hospital of birth. The study aimed to examine a possible link between IM Vitamin K administered to neonates and the development of cancer in childhood amongst the subjects. In total 664 cases were diagnosed with all cancers and the unadjusted OR was 0.89 (95% CI 0.69-1.15). However, the study recorded a raised OR for ALL (n=144) developing between one and six years after birth at 1.79 (95% CI 1.02-3.15). The results provided no evidence of the association that the study investigated, however the authors did not contest the suggestion of previous studies that IM Vitamin K had the potential to increase the risk of childhood cancer.

In 1998, the Department of Health (DoH), UK, commissioned a pooled analysis of individual patient data from six studies. The six studies were conducted in the UK and in Germany. These studies compared children who were given IM Vitamin K at birth and developed childhood cancer with children who were matched for either place or hospital of birth and date and who were never diagnosed with cancer. Case children included those who developed cancer before 15 years of age (n=2,431). They were matched by sex and year of birth (not place) with controls (n=6,338). Two types of analysis were conducted as in many cases records were not found in stored medical notes. Hence the first analysis assumed that in case of missing written records, Vitamin K was not given and for the second analysis, where written records of administration

were missing, hospital policy and perinatal morbidity information facilitated 'impute' of whether or not Vitamin K had been administered. The first analysis did not yield any association between childhood cancer and neonatal administration of IM Vitamin K. The mode of delivery-admission to special care baby unit- and low birth weight-adjusted OR was 1.09 (95% CI 0.92-1.28) for leukaemia and 1.05 (95% CI 0.92-1.20) for other cancers. The second analysis reported an increased adjusted OR of 1.21 (95% CI 1.02-1.44) for leukaemia and 1.10 (95% CI 0.95-1.26) for other cancers. The results showed that solid tumours were not more common in children who were given IM Vitamin K although results on childhood leukaemia remained unclear. Increased risk, if real, was found to be small at unadjusted OR of 1.25 (95% CI 1.06-1.46). The pooled analysis did not provide evidence that administration of IM Vitamin K was associated with childhood leukaemia. The lack of clarity on childhood leukaemia from this analysis was because this was not a controlled trial and it was suggested that clarity could be achieved by conducting an unrealistically large controlled trial.

The most recent study identified for the purpose of this epidemiological review was published in 2003 in the UK. This national case-control study examined the association between neonatal administration of IM Vitamin K and the subsequent development of leukaemia or other cancers. The study used abstractions from obstetric and neonatal records. Subjects/cases included children diagnosed with cancer before their 15th birthday (n=2,530), of whom 1,174 had leukaemia. Recruits also included control children without diagnosis of cancer (n=4,487).
Overall, IM Vitamin K administration records were available for 39% of the cases and 42% of the controls. There were no records for 24% of the cases and 22% of the controls regarding whether they had ever been given IM Vitamin K. The study found no link between IM Vitamin K administration and leukaemia or any other cancer as a group (OR 1.0). It concluded that there was not sufficient evidence to prove that Vitamin K, regardless of the route by which it was administered, influenced the development of childhood leukaemia or any other cancer. The results of this study, regarding the lack of association between IM Vitamin K administration and childhood leukaemia, were consistent with several previous studies.

A case-control study was conducted in Lower Saxony, Germany to assess the potential risk factors of childhood leukaemia. Subjects were registered patients at the German Children's Cancer Registry (GCCR). For each subject with leukaemia, diagnosed from 1988 to 1993, there were two (local and state) population-based controls and one tumour control. The study explored the potential association between parenteral Vitamin K prophylaxis and tumours or leukaemia. Self-administered questionnaires were provided to 435 parents of children with leukaemia and to parents of children who were not diseased (n=610). Results did not reflect a significant association between parenteral Vitamin K prophylaxis and tumours or leukaemia. The study recognized that Golding’s study results prompted the use of oral Vitamin K; however this had come to be regarded as an insufficient type of prophylaxis. The authors of this study, Kaatsch et al., therefore suggested that given their results and those of previous studies, administration of oral Vitamin K should be ceased and that of parenteral Vitamin K should be resumed.
In three hospitals in the south of England, a medical record-based study was carried out. Subjects included those who were diagnosed with leukaemia and non-Hodgkin's lymphoma (NHL) before they had reached the age of 30 years. Subjects included cases (n=177) and controls (age- and sex-matched; n=354).
The study found no association between leukaemia in childhood and neonatal administering of IM Vitamin K, OR 0.6 (95% CI 0.3-1.4) for ALL diagnosed between 1 and 6 years of age.

This epidemiological review identified twenty studies, including one pooled analysis, which reported the risk of leukaemia in children who were administered IM Vitamin K.
The literature search was conducted in PubMed without any date restrictions and in the English language. The studies included in this review were largely from the UK and the rest were from

Germany, Denmark, Sweden and the USA. Studies were largely population-based. Studies covered in this review included only newborn babies/children as their subjects. Most studies were case-control studies. The studies identified in this area were mostly conducted in the decade of 1990 and early 2000s, during a period when there were extensive debates about the safety of use of IM Vitamin K in newborn babies.
The total size of the study population covered in this review is approximately 2,345,422. The average size of the study population in the review is 156,361. The largest study population size reported is 1,384,424 and the smallest study comprised 531 subjects.
The increased risk of all cancers, leukaemia, ALL, etc. combined, was represented by ORs which ranged between 0.47 and 2.85. ORs of 2.85 and 1.97 were outliers as they were results of the two small studies, i.e., of Golding et al. (1990 and 1992), that reported an increased risk of childhood cancer in children who had been given IM Vitamin K. The study by Parker et al. reported a raised OR for ALL only at 1.79 for those aged 1-6 years. It concluded that there was no further evidence of the association being investigated, but also did not contest the suggestion of previous studies that IM Vitamin K had the potential to increase the risk of childhood cancer. Notwithstanding these ORs and borderline suggestions, the range of ORs then remained between 0.47 and 1.70 for majority of the studies that concluded that there was no association between childhood cancer and administration of IM Vitamin K.
The studies conducted after the hypothesis generating studies by Golding et al (1990 and 1992) provided no evidence of an association between the administration of IM Vitamin K and the subsequent development of childhood cancer or leukaemia.

For completeness, the Roche global drug safety database (ARISg) was searched for cases reporting events related to the high-level group term (HLGT) 'leukemia' and the high-level term 'white blood cell analysis', in patients who received treatment with phytomenadione (suspect drug), using a cutoff date of 15 March 2012. The ARISg search was carried out using the MedDRA version 14.1.

Based on the search criteria mentioned in the methodology section, two cases were retrieved from the ARISg database. No cases were retrieved for the HLGT 'leukemia'.
For one case (PT white blood cell count increased), which was serious, the patient was a newborn who received phytomenadione (oral administration) and was diagnosed with possible sepsis. The outcome was recovering/resolving.
The second case, (PT white blood cell count abnormal), which was non-serious, concerns a female (age unknown) who received phytomenadione (intravenous administration) for hepatic cirrhosis and needed a liver transplant.
In both cases, there was no association between IM phytomenadione and leukaemia.

Conclusion
A thorough literature search, an epidemiological review and a search of the Roche safety database provided no evidence of an association between the administration of IM Vitamin K and the subsequent development of childhood leukaemia. The literature search revealed that all relevant studies published were unable to confirm a link between IM Vitamin K and childhood leukaemia as suspected by Golding *et al*. The epidemiological review supports the findings of the literature review. There were also no childhood leukaemia related cases retrieved from the Roche safety database. It is of note regarding the epidemiological review, that the MHRA commented during the assessment (*Day89_PdAR_Phytomenadion_30_03_2012*) of the initial submission for this procedure that:
"*An Expert Working Group was then formed to review all the available studies and the Group considered that the evidence suggested that there was no increased risk of solid tumour in association with vitamin K and that there was no basis for recommending a change to the current licensing position of Konakion*."

In conclusion the totality of the available evidence does not alter the benefit-risk ratio of using IM Vitamin K. No change to the product label is warranted.

Assessor's comment
MAH has submitted an extended review on available studies. The potential risks have been widely discussed in scientific committees in various countries, there are no new studies indicating increased risk. Issue resolved.

QUESTION 2:
MAHs are also invited to provide information on studies concerning Vitamin K dosage in treatment of children with haemorrhage.

All study reports on Konakion clinical trials listed in the archives of the MAH were reviewed. None of the documents reported a clinical trial describing the Konakion treatment of children with haemorrhage.

A literature search was conducted on the following databases: Biosis Preview, Current Contents, Derwent Drug File, Embase, International Pharmaceutical Abstracts, Medline, Pascal and SciSearch with the key words "*Vitamin K, children and haemorrhage*" for publications between January 1980 and March 20, 2012.
(The submission includes Table 3 Publications on the Treatment of Haemorrhagic Paediatric Patients with Konakion).

Several studies have assessed the effect of administration of vitamin K to women prior to birth on the incidence of ICH in their neonates. In open label studies the frequency of severe forms of ICH (grades III and IV) seemed to be significantly lower in the treatment groups. However in more recent double blinded trials documented, antenatal vitamin K was not shown to be beneficial in preventing ICH in the newborn. Therefore vitamin K prophylaxis with oral or intramuscular administration of vitamin K given immediately after birth and early treatment with intravenous vitamin K are important treatment options for these very serious diseases in the newborn. There are, however, still controversial discussions about the most appropriate dose for newborns, particularly for the treatment of children suffering from severe haemorrhages. Because of the serious neurological complications of an existing haemorrhage most paediatricians advise that vitamin K should be administered rapidly at intravenous doses of 1 – 2 mg to these patients irrespective of the etiology, in addition to fresh frozen plasma or prothrombin complex concentrate.
Considering the seriousness of the disease and the relative rare incidence of haemorrhages in neonates, there are appropriate ethical reasons for the lack of clinical studies that would fulfil the needs of controlled clinical trials. The literature search conducted to provide additional information on the doses used to treat neonates with late onset vitamin K deficiency bleeding (VKDB), and presenting with an acute intracranial haemorrhage, did not identify controlled clinical trials.
However, several case reports were identified. In the majority of these reports the dose administered to the neonate was not provided. In the few publications where doses were stated (Danielson (2004), Merelle (2001), Saint Martin (1995), Choo (1994), and Verity (1983) the dose was in agreement with that of 1 – 2 mg stated in the Company International Standard Information (ISPI). It is important to note that in these patients vitamin K is normally administered, together with fresh frozen plasma or prothrombin complex concentrate. Doses and frequency of administration may vary considerably take into account the clinical situation and the

need of the paediatric patient. Due to the low toxicity of vitamin K the actual dose for this emergency treatment is not considered as being critical, but therapy with vitamin K should start as soon as possible.

The MAH is of the opinion, that the available evidence does not alter the benefit-risk ratio of using i. v. vitamin K as stated in the ISPI. No change to the product label is warranted.

Assessor's comment
Issue resolved.

QUESTION 3:
The Rapporteur noted that vitamin K is also licensed for the treatment of overdose with coumarin anticoagulants in children.
MAHs are requested to provide all available evidence on the use and posology of vitamin K dosage in reversal of coumarin anticoagulation with the intention to propose the inclusion of this indication in SmPCs across EU.

All study reports on Konakion clinical trials listed in the archives of the MAH were reviewed. None of the documents reported a clinical trial describing the treatment of overdose with coumarin anticoagulants in children.

A literature search was conducted on the following databases: Biosis Preview, Current Contents, Derwent Drug File, Embase, International Pharmaceutical Abstracts, Medline, Pascal and SciSearch on March 28, 2012 using the key words "Vitamin K, coumarin anticoagulants, and infants " for the time between January 1980 and March 28, 2012. During the time period included in the literature search no publications were identified, reporting study results on the treatment of overdoses with coumarin anticoagulants in pediatric patients using vitamin K.

Assessor's comment
The Applicant provided detailed historical background for inclusion of the treatment of overdose with coumarin anticoagulants in children in the United Kingdom and Ireland.

Generally they (children) require relatively higher doses of warfarin to achieve the desired anticoagulant effect. Streif *et al.* have shown that infants < 1 year of age require a daily dose of 0.33 ± 0.2 mg/kg while older children and adolescents require 0.09 ± 0.05 mg/kg to maintain a target INR of 2 – 3. Dosing of oral anticoagulants can be problematic in children younger than 6 months to a year for several reasons, since they usually have complex underlying health problems and are on multiple medications. These patients also frequently develop intercurrent illnesses. Such confounders of stable therapy are further compounded by the dietary challenges associated with breast versus bottlefeeding and the introduction of solid food.
Breast-fed infants are sensitive to oral anticoagulants because of the minimal vitamin K content in breast milk, whereas formula-fed infants require relatively higher doses of oral anticoagulants because of the vitamin K supplementation. These dietary issues complicate the achievement of stable therapy as they significantly impact upon vitamin K intake, making determination of required warfarin doses very difficult.
The relatively low numbers of children requiring therapy with vitamin K antagonists has hindered the conduct of clinical trials and resulted in the extrapolation of recommendations from trials in adults. Due to the lack of clinical trials, guidelines for anticoagulation treatment as well as current therapeutic INR ranges in children are widely extrapolated from recommendations for adults.

The validity of this approach is uncertain because of the significant effects of age on the coagulation system. For several reasons anticoagulant therapy in children is more difficult and requires more frequent monitoring compared with therapy of adult patients. Relatively rapid INR fluctuations due to intercurrent illnesses, variation in medication and changes in diet occur more often than in adults. The risk of serious bleeding in children receiving vitamin K antagonists for mechanical prosthetic valves is approximately 3.2% per patient-year. The risk increases significantly when the INR is > 8. Bleeding complications can be serious and life-threatening and treatment depends on the INR and degree of bleeding at presentation.
Furthermore, data from controlled clinical trials investigating the treatment of oral-anticoagulant-induced bleeding are not available. Several Treatment Guidelines however, suggest therapies which always include the recommendation that vitamin K is administered. Depending on the clinical situation fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) may also have to be added. As detailed above there are only limited data available in children and therefore these treatment guidelines for pediatric patients were derived from guidelines for adult patients. The vitamin K dose suggested in these guidelines is 30 µg/kg (for asymptomatic INR > 8) and is taken from a short communication by Bolton- Maggs. Furthermore, administration of phytomenadione for reversal of coumarin anticoagulation is the standard method of care as stated in the current issue of the BNF for Children, with dosing recommendations depending on symptoms.
In summary, the MAH is of the opinion that the current ISPIs reflect all available evidence on the use and posology of vitamin K dosage in reversal of coumarin anticoagulation and as such proposes the retention of the existing wording in the ISPIs.

Assessor's comment
It is recognized that increasing numbers of children require oral anticoagulation to prevent or treat thrombembolic complications. Warfarin competitively inhibits vitamin K resulting in low plasma concentrations of factors II, VII, IX and X, thus prolonging PT.
Monitoring of oral anticoagulation in children is difficult and requires close supervision. Bleeding is the main complication. Minor bleeding occurs in approximately 20%. When vitamin K is used to reverse warfarin effect, its dose is guided by the urgency and the anticipated need to resume long-term anticoagulation later.
Although we endorse the request from the UK, in the view of clinical significance of this problem, no clinical studies have been provided and there is currently no evidence to recommend vitamin K dosage in reversal of coumarin anticoagulant overdose due to the absence of supportive clinical data.

QUESTION 4:
Dose recommendations should be further assessed before any final wording is endorsed and therefore we endorse the Rapporteur's conclusion that additional information regarding dose recommendations should be provided by the MAH.
The MAH should notably provide justifications regarding the choice of the doses (whether 2 or 1 mg) and the duration of treatment (whether a 3 dose regimen or a prolonged treatment up to 3 months or more). Furthermore, SmPC wording should be proposed accordingly, notably for sections 4.1 and 4.2.

Justification of proposed wording
This wording is based largely on a study by Greer *et al*. and the treatment schemes proposed by several national societies as listed in the next section. In Greer's trial 79 patients were treated with an oral dose of 2 mg Konakion MM at birth, which was repeated at 7 and 30 days of life. An additional 77 patients were treated with intramuscular doses of 1 mg Konakion at birth. Prothrombin time (INR), plasma vitamin K and PIVKA II were monitored at 14, 30, and 56 days of age. At the end of the study prothrombin times did not differ between the two groups. Mean

plasma vitamin K concentrations decreased in both groups over time, but were higher in the oral group at 14 and 56 days of life.
The authors concluded from their results that 2 mg oral doses of Konakion MM when given three times in the first 30 days of life maintains blood concentration of vitamin K for the first two months of life at a concentration equal to, or greater than that achieved with standard intramuscular prophylaxis. The third oral dose given at 30 days maintains the blood concentration of vitamin K for 56 days, by which time the blood concentration in the intramuscular group has decreased significantly.
Treatment schemes similar to the one documented in the publication by Greer *et al*.**:** were suggested by the following national societies or pediatric experts:

• Australia (National Health and Medical Research Council)**:** Three 2 mg oral doses given at birth, at age between 3 – 5 days and not later than 4 weeks after birth

• Austria (Austrian Pediatric Society)**:** Three 2 mg oral doses given at birth, at age between 4 – 6 days and at 4 to 6 weeks after birth. Vitamin K from parenteral nutrition should not exceed 5 – 10 µg/kg body weight/day

• British Columbia (Canadian Paediatric Society)**:** Three 2 mg oral doses given at time of first feeding, at age between 2 to 4 weeks and at 6 to 8 weeks after birth

• Germany (Dr. von Kries, University of Munich)**:** Three 2 mg oral doses given at birth, at age between 4 and 10 days and at 4 to 6 weeks after birth.

• New Zealand (MZNO Practice Guidelines): Three 2 mg oral doses given at birth, at age between 3 and 5 days and at 4 to 6 weeks after birth.

• Switzerland (Dr. Schubiger, Lucerne)**:** Three 2 mg oral doses given at day 1, day 4 and week 4 after birth

• United Kingdom (Northern Health and Social Care Trust)**:** Exclusively breast-fed babies: Three 2 mg oral doses given at birth, at 1 week of life and at 4 to 6 weeks after birth.

The MAH proposes the following wording for sections 4.1 and 4.2 of the SmPC, as already included in the existing ISPI:
4.1 Therapeutic indications
Prophylaxis and treatment of haemorrhagic disease of the newborn.
4.2 Posology and method of administration
Dosage and administration
Prophylaxis
For all healthy neonates:
2 mg orally at birth or shortly after birth, followed by a further 2 mg dose four to seven days later.
A single 1 mg (0.1 ml) dose i.m. 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.
Exclusively breast-fed babies:
In addition to the recommendations for all neonates, 2 mg orally should be given after four to six weeks.

Assessor's comment

There is ongoing debate about the most appropriate regimen for prophylaxis of VKDB. The UK noticed that in the submitted studies, surrogate markers are used to assess the effect of different oral phytomenadione dosing schedules. The reason for that is that the incidence of vitamin K deficiency bleeding (VKDB) is very low and therefore designing a randomized controlled trial with late VKDB as an endpoint is virtually impossible. We agree that the main endpoint of the studies should be prevention of VKDB, both early and late. Comparison of different oral regimens would require hundreds of thousands of infants given the low incidence of VKDB, furthermore, it would be necessary to know the basal incidence of VKDB in population prior to any treatment to evaluate the effect.
Therefore the comparison of evidence from published surveillance studies remains.

Based on the review of submitted data the Rapporteur supports the opinion that 2 oral doses of vitamin K do not provide complete protection from VKDB in breastfed infants whose oral intake of vitamin K is low. The average vitamin K concentration ranges from 1 - 4 micrograms/L in human milk.They remain at an increased risk of late VKDB using this regimen.
Current ISPI section 4.2 of Konakion MM address this situation and recommends giving the third oral dose for exclusively breast-fed babies.
We are, however, concerned about the term "exclusively breast-fed", as there are cases when babies are "almost exclusively breast-fed" or "partially breast-fed". These infants would also remain at an increased risk and need vitamin K supplementation. Formula milk contains on average 40 – 50 micrograms of vitamin K per liter thus providing daily supplementation for formula fed babies (approximately 40 -50 micrograms/day vs. 1-4 micrograms/day in breast-fed infants). Studies show that VKDB in formula fed infants is very rare, and daily low doses may be "protective".

In draft decision of PdAR the Rapporteur recommended to change wording as follows:

4.2 Posology and method of administration
Dosage and administration
Prophylaxis
For all healthy neonates:
2 mg orally at birth or shortly after birth, followed by a further 2 mg dose four to seven days later and 2 mg dose after four to six weeks. The third dose is not required in infants predominantly formula fed.
A single 1 mg (0.1 ml) dose i.m. 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.
~~Exclusively breast-fed babies:~~
~~In addition to the recommendations for all neonates, 2 mg orally should be given after four to six weeks~~

Several studies from Germany (Von Kries et al, 2003), The Netherlands (Van Hasselt et al, 2007), UK (Pereira et al, 2003) have shown that oral prophylaxis is inefficient in patients with cholestatic liver disease and fat malabsorption. Current dosage recommendations for these patients in section 4.2 may be confusing: "1 mg i.m. or i.v. at birth or shortly after birth <u>if the oral route is unsuitable</u>" and the clinician may have an impression that oral route using 2 or 3 oral doses might be sufficient.
The Rappourter recommends to include warning: There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease.

Neonates with special risk factors (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics):

- 1 mg i.m. or i.v. at birth or shortly after birth if the oral route is unsuitable. There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease and malabsorption.
- i.m. and i.v. doses should not exceed 0.4 mg/kg (equivalent to 0.04 ml/kg) in premature infants weighing less than 2.5 kg.
- The size and frequency of further doses should be based on coagulation status.

QUESTION 5:
Dosing errors, more precisely parents having administered daily doses of vitamine K1 instead of weekly doses. This represents a risk of overdose.
Fortunately, no adverse events or only a few cases considered as medically not relevant have been reported.
Several measures have been taken:
- amendment of the patient leaflet in order to improve the comprehension of the posology by parents,
- addition of a warning for exclusively breast-fed infants on the packaging,
- communication to health care professionals regarding correct drug utilisation.
However, we are still receiving reports of dosing errors.
We would be interested to know whether such issue exists or not in other European countries and how they handle this unusual mode of administration.

The Roche global drug safety database (ARISg) was searched for cases concerning events related to Konakion (phytomenadione) in neonates, infants and children (birth to <12 years) and reported events related to the preferred terms of: “overdose”, “drug administration error”, “inappropriate schedule of drug administration”, “incorrect dose administered”, “incorrect drug administration duration”, “incorrect drug administration rate”, “incorrect drug dosage form administered”, “wrong drug administered”, “accidental exposure”, “drug prescribing error”, “medication error”, “product dosage form confusion”, and “accidental overdose”. A cut-off date of April 15th 2012 was used. The ARISg search was carried out using the MedDRA version 14.1.

There were 841 cases retrieved from the Roche Safety Database Search and of these 841 cases, 810 were from France and 31 cases were from other European countries (with no specific trend or emphasis on one country).
Of the 841 cases, 695 were overdose, including 9 accidental overdose and 18 cases where overdose was reported concomitantly with one of the above mentioned medication error preferred terms. Of the remaining 146 cases, concerning medication errors (excluding the overdose cases mentioned previously), 130 were reported from France and 16 were from the rest of Europe. Paediatric patient exposure for France and for other European countries during the period of 2001 to 2011 remained stable, with no large peaks in exposure.

From the 695 cases of overdose, 680 cases were from France, with 15 cases of overdose from other European countries.

Clinical practice across the EU
Information about the actual general clinical practice on dose and route of administration of vitamin K is very limited. Only published information available for a few countries can be used to estimate clinical use and a reliable comparison of clinical practice in European countries as compared to France is fairly difficult. The correct vitamin K dose and the route of application for prophylaxis of vitamin K deficiency bleeding (VKDB) in neonates are still debated by pediatricians across Europe and in other countries of the world. Consensus only exists that one single 1 mg i. m. dose given shortly after birth prevents VKDB including the most serious form

late VKDB. Multiple oral doses might be similar in effectiveness to the parenteral administration but an optimal dose regimen still needs to be established. Therefore a range of oral treatment policies, national treatment guidelines and dose recommendations have been adopted. The approaches differ between several countries and so far they cannot totally prevent potentially lethal late VKDB. All oral dosing schemes effectively abolish all risks of early VKDB, which occurs in during the first 24 hours of life, as well as the classic form of VKDB, which is seen between days 1 and 7 of life. Critical is the efficacy in late VKDB, where considerable diferences between different treatment schedules have been observed.
The following recommendations for oral doses of vitamin K have been published in recent years:

• Australia (National Health and Medical Research Council)
Three 2 mg oral doses given at birth, at age between 3 – 5 days and not later than 4 weeks after birth

• Austria (Austrian Pediatric Society)
Three 2 mg oral doses given at birth, at age between 4 – 6 days and at 4 to 6 weeks after birth. Vitamin K from parenteral nutrition should not exceed 5 – 10 µg/kg body weight/day

• British Columbia (Canadian Paediatric Society)
Three 2 mg oral doses given at time of first feeding, at age between 2 – 4 weeks and at 6 to 8 weeks after birth

• Denmark (Dr. Hansen, Viborg-Kjellerup Hospital)
One 2 mg oral dose at birth and weekly 1 mg oral dose up to 3 months

• France (Dr. Autret-Leca, Hôpital Bretonneau, Tour)
Exclusively breast-fed infants: Two 2 mg oral doses and 25 µg/day or 2 mg/week during breast-feeding

• Germany (Dr. von Kries, University of Munich)
Three 2 mg oral doses given at birth, at age between 4 – 10 days and at 4 to 6 weeks after birth.

• New Zealand (MZNO Practice Guidelines)
Three 2 mg oral doses given at birth, at age between 3 – 5 days and at 4 to 6 weeks after birth.

• Switzerland (Dr. Schubiger, Lucerne)
Three 2 mg oral doses given at day 1, day 4 and week 4 after birth

• United Kingdom (Northern Health and Social Care Trust)
Exclusively breast-fed babies: Three 2 mg oral doses given at birth, at 1 week of life and at 4 to 6 weeks after birth.

In conclusion the majority of the reports of overdose and medication errors concern France, with the majority of these cases being non-serious, with no adverse events reported. From the results obtained from the Roche Safety Database search there are no other dosage error issues for any other European country. The MAH is of the opinon that a harmonized wording as proposed in Response to Question 4 will lead to a reduction in the overdose reported in France.

Assessor's comment
Although dosing guidelines for administration of oral vitamin K differ, currently in Latvia Konakion MM is administered by a health care professional (3 x 2mg oral regimen). We support the

opinion that these organisational issues should be agreed locally taking into account local circumstances and social reasons.
In countries that use very different regimens, e.g., low daily dose of 25 micrograms (following 1mg orally after birth) in The Netherlands, or 1 mg weekly (following 2 mg orally at birth) in Denmark, or 2 mg weekly (after 2 mg orally at birth) in France compliance for administration will always rely on parental input.

The Member States are welcomed to comment on this issue.

QUESTION 6:
Also, it would be interesting to compare the different packagings available in Europe. In France, VITAMINE K1 ROCHE 2mg/0.2ml NOURRISSONS, solution buvable et injectable allows to deliver a full dose of 2mg with a pipette and is conditioned in packages of 6 ampoules. Some packaging improvements might be envisaged.

Several changes have been made to the French pack to address the overdose cases which have been reported from France. Furthermore approximately 2 years ago Roche submitted a technical change globally, to register a pack of 5 ampoules and 5 dispensers. The MAH wishes to note that the 5 ampoule/5 dispenser pack is also now registered in France as of 12 September 2011 (replacing the 6 ampoule pack referred to by the assessor). The pack size and colours across Europe are harmonized in the new Roche family design, with clear colouring dedicated to the strengths (pink bar for paediatric, blue bar for adults) designed to distinguish the packs/strengths to avoid further delivery mistakes.

Assessor's comment
Issue resolved.

Further comments were received from Member States following the circulation of Day 90 updated PdAR to MSs with draft decision.

- *Member State Comment*

We acknowledge that there are limited data available on the use of Konakion as an antidote therapy to anticoagulant drugs in children; however we would like to emphasize that this indication was granted in UK in 2005, based on a thorough risk:benefit assessment, input from specialists and taking into account the significant clinical need. Therefore the UK intends to maintain the paediatric indication of "Antidote therapy to anticoagulant drugs of the coumarin type" with the already approved posology in the nationally approved SmPC.

Section 4.2:
We consider the proposed posology information in section 4.2 rather confusing and advise that a clear distinction should be made between premature infants weighing < 2.5 kg vs. premature infants weighing > 2.5kg vs. term infants. The Rapporteur's recommendation to clarify the method of infant feeding (breast milk vs. formula) is fully endorsed.
Consequently we recommend the following wording for consideration in section 4.2 of the SmPC:

*"**Healthy neonates of 36 weeks gestation and older**:*

Either:
1mg administered by intramuscular injection at birth or soon after birth
or
2mg orally at birth or soon after birth. The oral dose should be followed by a further dose of 2mg at 4-7 days of age. A further 2 mg oral dose should be given at 1 month after birth. In exclusively formula fed infants the third oral dose can be omitted.

Preterm neonates of less than 36 weeks gestation weighing 2.5kg or greater, and term neonates at special risk*: 1mg IM or IV 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 2.5kg: *0.4mg/kg (equivalent to 0.04ml/kg) IM or IV 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.*

There is evidence that oral prophylaxis is insufficient in patients with underlying cholestatic liver disease and malabsorption."

We would like to emphasize the importance of clear information for Konakion's parenteral method of administration as - due to the small volumes required - dosing errors are a widely recognized problem, especially in low birth weight premature infants. In the UK this issue was addressed by inserting a detailed dosing table with a specific caution in section 4.2 (see below for your reference). Other MSs may also consider that similar measures are indicated.

"CAUTION: care is required when calculating and measuring the dose in relation to the baby's weight (10 times dosing errors are common).

Dosing information for preterm babies at birth for the prophylaxis of VKDB

Weight of the baby	***Dose of vitamin K at birth***	***Injection volume***
1kg	*0.4mg*	*0.04ml*
1.5kg	*0.6mg*	*0.06ml*
2kg	*0.8mg*	*0.08ml*
2.5kg	*1mg*	*0.1ml*
Over 2.5kg	*1mg*	*0.1ml*

Assessor's comment
Indication "Antidote therapy to anticoagulant drugs of the coumarin type".
The Rapporteur holds the position that although we endorse the request, no clinical studies have been provided and there is currently no evidence to recommend vitamin K dosage in reversal of coumarin anticoagulant overdose due to the absence of supportive clinical data.
Study data in adults indicate the efficacy of vitamin K, but is not sufficient to authorise paediatric use. Further studies would be very valuable and MAHs are recommended to conduct such studies.
As described in Pediatric Worksharing guide it is not the aim of Article 45 procedure to remove existing paediatric indications for products which are already in clinical use in particular member states, and vitamin K is the key substance in reversal of coumarin anticoagulation.

Therefore it is not requested to remove the existing indication in concerned Member States.

The proposed posology.
The Rapporteur agrees to the recommended wording and proposes additional cross-reference to section 5.1. to provide more information on the available evidence regarding cholestasis. Special risk factors are further described.

Data on effectiveness of oral prophylaxis in patients with cholestasis
Intestinal absorption of mixed micellar phylloquinone (vitamin K_1) is unreliable in infants with conjugated hyperbilirubinaemia: implications for oral prophylaxis of vitamin K deficiency bleeding, Pereira et al 2003
Objective: To compare the pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease, a known risk factor for VKDB.
A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinaemia (idiopathic neonatal hepatitis - 17 patients, biliary atresia - 13, total parenteral nutrition cholestasis - 3, Alagille's syndrome -2, alpha 1 antitrypsin deficiency - 2, inspissated bile syndrome - 2, and 5 miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis).
Main outcome measures were serum concentrations of vitamin K1 and undercarboxylated prothrombin (PIVKA-II; a sensitive functional indicator of vitamin K status) before and for up to four days after a single dose of mixed micellar K1 1 mg intravenously or 2 mg orally.
Comparison of K1 levels 24 hours after oral K1 with those from 14 healthy newborns given the same dose.

Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K1 concentrations, indicative of subclinical vitamin K deficiency. Median serum K1 concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K1 but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K1 compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum K1 > 10 ng/ml.

Conclusions: The intestinal absorption of mixed micellar K1 is unreliable in infants with conjugated hyperbilirubinaemia. Given the strong association between cholestasis and late vitamin K deficiency bleeding, these data provide an explanation for the failure of some oral vitamin K1 prophylaxis regimens in infants with latent cholestasis.

Proposed wording in
Section 5.1
Paediatric population
A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinaemia (idiopathic neonatal hepatitis - 17 patients, biliary atresia - 13, total parenteral nutrition cholestasis - 3, Alagille's syndrome -2, alpha 1 antitrypsin deficiency - 2, inspissated bile syndrome - 2, and 5 miscellaneous diagnoses (fructosaemia, galactosaemia, choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis). The pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease was compared.
Main outcome measures were serum concentrations of vitamin K1 and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar K1 1 mg

intravenously or 2 mg orally. Comparison of K1 levels 24 hours after oral K1 with those from 14 healthy newborns given the same dose.
Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K1 concentrations, indicative of subclinical vitamin K deficiency. Median serum K1 concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K1 but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K1 compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum K1 > 10 ng/ml.

- *Member State Comment*

We do not agree with the overall conclusions of the Rapporteur for the following reasons:

The proposal of the MAH and the new proposal of the RMS to change the dose recommendations in the section 4.2 of the SmPC concerning prophylaxis (2-dose regimen by formula fed infants instead of currently recommended 3-dose regimen) are problematic and are therefore not endorsed:

The MAH recommends the third oral dose of 2 mg vitamin K after 4-6 weeks only in case of „exclusively breast-fed babies". As noticed by the RMS, this wording could be confusing for the parents as there are „almost exclusively" or „partially breast-fed" cases too, in which the infants may still need the third oral dose of 2 mg vitamin K supplementation.
The RMS proposes to change the wording into „The third dose is not required in infants predominantly formula fed".

The new proposed wording of the RMS however, could also be ambiguous, as there is no clear definition of „predominantly" (how many times, in which time intervals?); the infants, who may be in need of the third dose, could get excluded.

In the majority of the Member States the 3-dose regimen is the standard recommendation for the prophylaxis of VKDB by the healthy infants, regardless of the mode of nutrition. The third oral dose has not been reported to be an issue of safety concern in formula fed infants. The MAH is invited to present supporting literature in this regard, if available.
Otherwise the risk of bleeding (omission of the third dose) could overweigh the risk of probable vitamin K overdose which might arise from the third recommended dosage, given that such an overdose has ever been documented. The majority of overdose cases (all-cause) and medication errors were non-serious, with no adverse events reported (Roche global drug safety data base). Therefore, the risk-benefit ratio of the proposed text changes in the section 4.2 concerning prophylaxis dosages is negative.

Assessor's comment
Data on effectiveness of oral prophylaxis with Konakion MM.
Breastfeeding is recognized as a major risk factor for late VKDB. This is presumably because of a lower vitamin K intake in breastfed infants: whereas human milk contains 1 - 2 µg/L, most infant formulas are artificially fortified and contain 50 µg/L. A
have been advised to prevent VKDB in breastfed infants. A single intramuscular dose of vitamin

K at birth is considered most efficacious, oral administration of vitamin K at birth prevents classical VKDB but is less effective in late VKDB.

A prospective 6-year surveillance study from Switzerland (*Prevention of vitamin K deficiency bleeding with oral mixed micellar phylloquinone: results of 6-year surveillance in Switzerland, Schubiger et al 2003*) assessed the efficacy of 2 mg oral vitamin K (Konakion MM) given twice (on the 1st and 4th day). Over a period of 6 years (475,000 deliveries) there were no cases of early (<24 h of age), 1 case of classical (2-7 days of age) and 18 cases of late (1-12 weeks) VKDB fulfilling standard case definitions. The incidence of late VKDB for infants with completed Konakion MM prophylaxis (2 oral 2 mg doses) was 2.31/100,000 (95% CI :1.16-4.14) and for the entire population 3.79/100,000 (95% CI:2.24-5.98). In 13/18 patients with late VKDB there was pre-existing liver disease. There was only one case of late VKDB after recommended prophylaxis (oral 2 mg x2) in a fully breast-fed infant without underlying liver disease.

This study shows the effectiveness of 2 oral 2 mg doses (given on 1st and 4th day). 19 definite VKDB cases of 475'372 infants, 11 had received their vitamin K prophylaxis in accordance with the recommendations, all patients were partially (n=2) or fully breast-fed (n=16). Of all reported cases there were 2 partially breast-fed patients who received 2 oral doses of 2 mg Konakion MM and failed oral prophylaxis. These patients had underlying hepatic disease - biliary atresia, cholangitis.
It should be added in the end that authors recommend to include the 3rd oral dose at 4 weeks of age.

Another study by Hasselt et al 2008 (*Prevention of vitamin K deficiency bleeding in breastfed infants: lessons from the Dutch and Danish biliary atresia registries, Hasselt et al 2008*) compared the risk of VKDB under different prophylactic regimens in high-risk population - infants with biliary atresia. In a retrospective cohort study in Dutch and Danish infants with biliary atresia VKDB was noted in 25 of 30 of breastfed infants on 25 µg of daily oral prophylaxis, in 1 of 13 on 1 mg of weekly oral prophylaxis, in 1 of 10 receiving 2 mg of intramuscular prophylaxis at birth, and in 1 of 93 formula-fed infants ($P < .001$). The relative risk of a bleeding in breastfed compared with formula-fed infants was 77.5 for 25 µg of daily oral prophylaxis, 7.2 for 1 mg of weekly oral prophylaxis, and 9.3 for 2 mg of intramuscular prophylaxis at birth.
Infants were categorized as “breastfed” if they had received exclusively breastfeeding from birth onward. All of the other infants were categorized as “formula fed.”
Authors compared the risk of (severe) Vitamin K deficiency and VKDB in breastfed infants receiving frequent oral or IM prophylaxis with the risk in formula-fed infants. Only 1 of the 93 formula-fed infants had a VKDB. Dutch breastfed infants were poorly protected against VKDB compared with formula-fed infants, with a relative risk for a VKDB of 77.5 (95% CI: 11.0–548.0). Similar results were obtained when only Dutch formula-fed infants were used for comparison (RR: 73.3; 95% CI: 10.4–518.0)

The effectiveness of 3 oral 2 mg doses in Germany has been evaluated in a study by von Kries et al 2003 (*Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding, R von Kries et al 2003*)
Study population were infants in Germany in 1997–2000, main outcome measure was confirmed VKDB between day 8 and week 12 and no condition requiring specific vitamin K supplementation known before the onset of bleeding.
Twenty nine reports met the case definition: 7 had not received any vitamin K prophylaxis; for 3, vitamin K prophylaxis was unknown; 2 had insufficient vitamin K prophylaxis for their age; 17 had been given the recommended doses. The mixed micellar preparation had been given to 7, other preparations to 9, and 1 had been given both. These cases did not differ with respect to the site of bleeding and cholestasis detected at bleeding. Estimates of the use of the MM

preparation in birth hospitals and by paediatricians yielded 1 817 769 newborns exposed to the mixed micellar preparation and 1 320 926 newborns exposed to other preparations. 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.
28 of 29 children had been exclusively breast-fed, breast + formula in 1 case. In 21/29 cases cholestasis was detected after the bleeding episode (3 bile duct atresia and bile duct hypoplasia, 2 cases of homozygous alpha 1 antitrypsin deficiency, 1 case of Byler's disease and sclerosing cholangitis). In 17 cases, the recommended prophylactic doses of vitamin K according to age had been given.

Vitamin K-enriched formulas provide some protection against late VKDB, since the disease is seen almost exclusively in breastfed infants. Formula feeding supplies a regular dose.
In accordance with posology information provided by MAH Roche in majority of Member States the 3 dose regimen currently is licensed for exclusively breast-fed babies (except for Denmark, Finland and Norway where single IM dose at birth is licensed). For all infants who are not exclusively breast-fed the 2 dose regimen is recommended, unless they have special risk factors.
Studies on efficacy of VKDB prophylaxis (see above for your reference) show that proportion of children with cholestasis is high and majority were exclusively breast-fed. There are, however, several partially formula-fed infants.
The currently proposed posology (updated and clarified in accordance with the UK recommendations) would include all partially formula-fed infants who might need the 3rd dose, because their daily intake of vitamin K is still low, but allow avoiding unnecessary overdose in healthy formula-fed infants. Currently proposed wording recommends 3 dose regimen to all healthy infants, and takes into account the available evidence that formula-feeding is somewhat protective (Formulas are artificially fortified and bacteria that produce menaquinones - vitamin K2 are more common in formula-fed infants).

Due to the late stage of the procedure it was not able to ask MAH to provide supporting literature regarding overdose (3rd dose) concern in formula-fed infants. The rapporteur identified a study by Clarke et al 2006 (Vitamin K prophylaxis for preterm infants: a randomized, controlled trial of 3 regimens, Clarke et al 2006). Infants <32 weeks' gestation were randomized to receive 0.5 mg (control) or 0.2 mg of vitamin K_1 IM or 0.2 mg IV after delivery. Increased vitamin K epoxide in preterm infants receiving large amounts of vitamin K with no overt toxicity was found. The authors conclude that 'besides overloading the hepatic VKOR cycle, excessive vitamin K may overwhelm the hepatic pathway responsible for its catabolism and excretion. In neonates the terminal half-life for plasma clearance of vitamin K is considerably longer than in adults, whatever the route. This impaired elimination capacity may also be explained by the immaturity of organ and metabolic systems in preterm infants.'

- *Member State Comment*

We globally agree with the overall conclusion of the Rapporteur. However, we have the following additional comment.

The proposed dose regimen of 3 doses, at birth, day 4-7 and after 4 to 6 weeks, appears to provide a good supplementation through the first 12 weeks of life. There is no clear data from literature regarding the efficacy of the different dose regimen across countries for the prevention of late form of Vitamin K deficiency bleeding. However, the proposed dose regimen might be

insufficient in case of prolonged exclusive breast-feeding. Since there is no identified risk of overdosage, we suggest recommending an additional dose, the next month, in this situation.

Suggested additional wording in section 4.2:

In case of exclusive breast-feeding during more than 4 months, an additional dose of 2 mg could be given after 3 or 4 months.

Assessor's comment
Further doses in breast-fed infants.
Data on further weekly oral doses
Hansen KN, Minousis M, Ebbesen F. Weekly oral vitamin K prophylaxis in Denmark. Acta Pædiatr 2003; 92: 802-805.
The aim of the study was to evaluate oral vitamin K prophylaxis at birth by giving 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age.
Methods: A total of 507 850 live babies were born in Denmark during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. A survey of possible cases of vitamin K deficiency bleeding (VKDB) was carried out by repeated questionnaires to all Danish paediatric departments and by checking the National Patient Register.
Results: No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100000 (95% CI). The questionnaires were used to evaluate compliance with the regimen. Parents of 274 infants participated. A dose of vitamin K was regarded as having been given if the infant received a drop of vitamin K or was mostly formula-fed that week, and the prophylaxis was regarded as completed if the infant had received at least 9 doses. Compliance was good, with 94% of the infants completing the course of prophylaxis.

The Rapporteur proposes the following wording to be included in sections 4.2 and 5.1.

Section 4.2
Further oral doses in breast-fed infants have been advised, but safety or efficacy data for these additional doses is limited (see section 5.1).

Section 5.1
Paediatric population
The data from a retrospective study indicate that weekly oral prophylaxis was effective in the prevention of VKDB (Weekly oral vitamin K prophylaxis in Denmark, Hansen et al 2003). A total of 507 850 live babies were born in Denmark during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. Oral vitamin K prophylaxis at birth 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age. No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100000 (95% CI).

Following second circulation of updated PdAR the proposed changes were endorsed by other Member States with some minor changes in wording.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

The preliminary assessment report with a list of questions to the MAHs was circulated in March 2012, additional requests for information were received from several Member States. The Applicants were asked to provide further information on phytomenadione safety aspects regarding reported association of i.m. vitamin K and childhood leukemia, additional studies on the optimal dosage for treatment of vitamin K deficiency bleeding, evidence on the use and posology of vitamin K dosage in reversal of coumarin anticoagulation, the dosage in prophylaxis of haemorrhagic disease in newborns. The Applicant's response and assessment of available studies led to proposal of several variations in product information, therefore an updated assessment report was circulated in September 2012.

Several comments were received from Member States that led to implementation of more detailed dosing information in section 4.2 and cross-reference to section 5.1 to include information from paediatric studies.
During the procedure it was recognized that vitamin K is authorized also for treatment of coumarin anticoagulant overdose in several MSs, but no studies on the optimal dosage in paediatric population could be identified. However, study data in adults indicate the efficacy of vitamin K in reversal of coumarin anticoagulant overdose, the indication is of particular clinical importance, and it is not the aim of Article 45 procedure to remove existing indications, therefore it should not be removed in concerned MSs. Further studies are recommended to establish the most appropriate dosage.
There was also a concern regarding 3rd dose for oral prophylaxis of late VKDB in exclusively breast-fed vs. formula-fed infants. The available studies show that formula feeding is somewhat protective (formulas are supplemented with vitamin K) and after discussion between MSs it was proposed to include this information in SmPC.
In accordance with posology information provided by MAH Roche (originator) in majority of Member States the 3 dose regimen currently is licensed for exclusively breast-fed babies (except for 3 MSs where single IM dose at birth is licensed). For all infants who are not exclusively breast-fed the 2 dose regimen is recommended, unless they have special risk factors.
Studies on efficacy of VKDB prophylaxis show that proportion of children with cholestasis is high and majority were exclusively breast-fed. There are, however, several partially formula-fed infants.
The currently proposed posology includes all partially formula-fed infants who might need the 3rd dose, because their daily intake of vitamin K is still low, but allow avoiding unnecessary overdose in healthy formula-fed infants. Currently proposed wording recommends 3 dose regimen to all healthy infants, and takes into account the available evidence that formula-feeding is somewhat protective.

A question regarding further oral doses in exclusively breast-fed infants arose during discussion. There are different recommendations and guidelines in Member States. This practice has been evaluated in clinical studies, but the doses and frequency of administration vary a lot. No particular recommendation can be made, although the results are promising, therefore Product Information is updated, but safety or efficacy data for these additional doses is limited.

Upon finalization of the procedure Rapporteur's overall conclusions and proposed changes in Product Information were endorsed by all concerned Member States.

Recommendation

Type IB variation to be requested from the MAHs within 60 days of finalization.

The following information to be included in SmPC

4.2 Posology and method of administration
Dosage and administration

Healthy neonates of 36 weeks gestation and older:
Either:
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 4-7 days of age. A further 2 mg oral dose should be given at 1 month after birth. In exclusively formula fed infants the third oral dose can be omitted.
Preterm neonates of less than 36 weeks gestation weighing 2.5kg or greater, and term neonates at special risk (e.g. prematurity, birth asphyxia, obstructive jaundice, inability to swallow, maternal use of anticoagulants or antiepileptics): 1mg IM or IV 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 2.5kg: 0.4 mg/kg (equivalent to 0.04 ml/kg) IM or IV 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.

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

CAUTION: care is required when calculating and measuring the dose in relation to the baby's weight (10 times dosing errors are common).

Dosing information for preterm babies at birth for the prophylaxis of Vitamin K deficiency bleeding

Weight of the baby	Dose of vitamin K at birth	Injection volume
1 kg	0.4 mg	0.04 ml
1.5 kg	0.6 mg	0.06 ml
2 kg	0.8 mg	0.08 ml
2.5 kg	1 mg	0.1 ml
Over 2.5 kg	1 mg	0.1 ml

Further oral doses in breast-fed infants have been advised, but safety or efficacy data for these additional doses is limited (see section 5.1).

Section 5.1
Paediatric population
A prospective randomised controlled study included 44 infants (1-26 weeks of age) with conjugated hyperbilirubinaemia (idiopathic neonatal hepatitis - 17 patients, biliary atresia - 13, total parenteral nutrition cholestasis - 3, Alagille's syndrome -2, alpha 1 antitrypsin deficiency - 2, inspissated bile syndrome - 2, and 5 miscellaneous diagnoses (fructosaemia, galactosaemia,

choledochal cyst, necrotising enterocolitis, cytomegalovirus hepatitis). The pharmacokinetics and efficacy of oral versus intravenous mixed micellar vitamin K prophylaxis in infants with cholestatic liver disease was compared.
Main outcome measures were serum concentrations of vitamin K1 and undercarboxylated prothrombin (PIVKA-II) before and for up to 4 days after a single dose of mixed micellar K1 1 mg intravenously or 2 mg orally. A comparison was also made between K1 levels 24 hours after oral K1 administration with those of 14 healthy newborns given the same dose.
Results: At admission, 18 infants (41%) had elevated levels of serum PIVKA-II and eight (18%) had low K1 concentrations, indicative of subclinical vitamin K deficiency. Median serum K1 concentrations were similar in the oral and intravenous groups at baseline (0.92 v 1.15 ng/ml), rising to 139 ng/ml six hours after intravenous K1 but to only 1.4 ng/ml after oral administration. In the latter group, the low median value (0.95 ng/ml) and wide range (< 0.15–111 ng/ml) of serum K1 compared unfavourably with the much higher levels (median 77, range 11–263 ng/ml) observed in healthy infants given the same oral dose, and suggested impaired and erratic intestinal absorption in cholestatic infants. The severity of malabsorption was such that only 4/24 (17%) achieved an incremental rise in serum K1 > 10 ng/ml.

The data from a retrospective study indicate that weekly oral prophylaxis was effective in the prevention of VKDB. A total of 507 850 live babies were born during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. Oral vitamin K prophylaxis at birth 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 months of age. No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100000 (95% CI).

The following information to be included in PIL section 3:

<Phytomenadione> can be given to your child by injection into a vein or muscle or by mouth. How it is given will depend upon what the medicine is being used for and whether your baby was born prematurely.

Prevention of vitamin K deficiency bleeding
Healthy babies delivered at or nearly full term
These babies will be given either:
• A single injection (1 mg) either at birth or soon after, or
• By mouth (oral) a first dose (2 mg) at birth or soon after. This is followed by a second 2 mg dose after 4 to 7 days and third 2 mg dose at 1 month. In exclusively formula fed infants the third oral dose can be omitted.

Premature babies or full term babies at special risk of bleeding
• These babies will be given <phytomenadione> as an injection at birth or soon after.
• More injections may be given later if your baby is still at risk of bleeding.

Further doses:
• Babies who are given vitamin K by mouth and who are breast-fed (not given formula milk) may need more doses of vitamin K by mouth.
• Bottle-fed babies given the two doses of vitamin K by mouth may not need any more doses of vitamin K. This is because it is included in formula milk.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Roche, Konakion 2 mg/0.2 ml and Konakion 10 mg/ml
InfectoPharm, KA-VIT