

NEOKAY 1MG CAPSULES

PL 04532/0012

UKPAR

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NEOKAY 1MG CAPSULES

PL 04532/0012

Introductory Note to Reader

This Public Assessment Report produced by the MHRA is written in the form of a date or time-based commentary on the assessment of the application for Marketing Authorisation made by the Applicant. The document must therefore be read in its entirety in order to gain a complete and accurate understanding and awareness of the application made, the assessment procedure and outcomes, the resolutions of any issues and the conclusions reached.

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted BioMedical Services Ltd., a Marketing Authorisation (licence) for the medicinal product Neokay 1mg Capsules (PL 04532/0012) on 15th February 2010. This is a prescription-only medicine (POM) used to prevent vitamin K deficiency bleeding in babies.

Neokay 1mg Capsules contains the active ingredient phytomenadione (synthetic vitamin K). Vitamin K is essential in the body for blood to clot. Newborn babies can have too little Vitamin K and so may develop a serious, but rare condition that causes bleeding. Neokay is used to prevent your baby from developing a tendency to bleed due to a deficiency in vitamin K.

The Applicant demonstrated that Neokay 1mg Capsules had no unexpected safety concerns and it was therefore judged that the benefits of taking Neokay 1mg Capsules outweigh the risks; hence a Marketing Authorisation has been granted.

**NEOKAY 1MG CAPSULES
PL 04532/0012**

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Note: This assessment report has been updated to incorporate information provided by the Applicant in response to queries raised by the assessor and/or the Commission on Human Medicines during the assessment process. Updates are generally not included at the point where queries are raised but in later appropriate sections. Please therefore read the entire document in order to obtain full information. Please note however that all queries raised by the assessors and the Commission on Human Medicines were answered satisfactorily by the Applicant, as presented in the section “Committee on Safety of Medicines recommendations and assessments of applicant responses”.

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Neokay 1mg Capsules (PL 04532/0012) on 15th February 2010. The product is a prescription-only medicine.

This application was made under Article 10a of Directive 2001/83/EC, so called well-established use, and as such this application relies solely on bibliographic data with respect to the clinical aspects.

Vitamin K is an essential co-factor in the hepatic synthesis of prothrombin (factor II) and of several other blood clotting factors (factor VII, IX, X and the coagulation inhibitors protein C and protein S). Low levels at birth may lead to the development of a generalised bleeding tendency (haemorrhagic disease of the new born). Vitamin K deficiency bleeding (VKDB) was described over 100 years ago and was then termed haemorrhagic disease of the newborn (HDN)

Phytomenadione (vitamin K) is a fat soluble vitamin which does not cross the placenta readily. There is relatively little in human milk. Cow's milk contains more, and infant formula milks are artificially fortified. The half life in plasma is 2-3 hours. Vitamin K is absorbed from the small intestine and taken up by the liver but is only stored in the body for relatively short periods of time. Intra-muscular administration of phytomenadione in an emulsion may aid retention by setting up a “depot” muscle store. Bile salts aid absorption. The mixture of short and medium chain triglycerides contained in the Neokay formulation is readily absorbed, even in the absence of biliary and pancreatic secretions. The drug is metabolised to more polar metabolites and excreted in the urine and bile as glucuronide and sulphate conjugates.

Neokay 1mg Capsules are indicated for the prevention of vitamin K deficiency bleeding in babies

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Phytomenadione

Nomenclature

INN: Phytomenadione

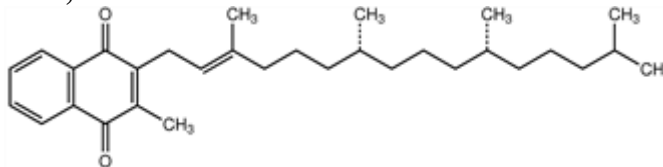
Chemical Name:

2-Methyl-3-[3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione

Molecular Formula

C₃₁H₄₆O₂

Molecular Structure;



MW: 450.7

CAS Number: 84-80-0

General Properties

A clear, intense yellow, viscous oily liquid, which decomposes on exposure to actinic light. Practically insoluble in water; sparingly soluble in alcohol; miscible with fatty oils.

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacturer.

An appropriate specification is provided for the active substance phytomenadione.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

An impurity profile for the drug substance has been provided and the impurities are identical to those in the British Pharmacopoeia for phytomenadione.

Active phytomenadione is stored in appropriate packaging material. The specifications and typical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

An adequate re-test period has been defined based on the conducted stability studies.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely fractionated coconut oil (containing at least 95% of saturated 8 and 10 carbon atom fatty acids) within the body of the capsule. The fractionated coconut oil is in compliance with its Ph Eur monograph.

The soft capsules shell consists of gelatin, glycerol, iron oxide red (E172), iron oxide black (E172) and purified water. All the ingredients within the capsule shell comply with their respective Ph.Eur monograph with the exception of iron oxide red (E172), iron oxide black (E172), in the absence of Ph Eur monographs comply with in-house specifications and comply with Directive 95/45/EC use of colours in foodstuffs. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients used contain material of animal or human origin. The suppliers of gelatine have provided certificates to show compliance with current regulations concerning the minimising of transmission of BSE/TSE in their products.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is packaged in polypropylene plastic bottles with low density polyethylene/high density polyethylene (LDP/HDP) caps. The finished product is packaged in pack sizes of 12 or 100. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Do not store above 25oC” “Do not freeze” and “Store in original package”.

Summary of Product Characteristics

This is acceptable.

Patient Information Leaflet

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Label

This is acceptable.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of the product are well- known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.

CLINICAL ASSESSMENT

1. SUMMARY

This is an abridged product licence application for a liquid formulation of phytomenadione (Vitamin K) for administration to neonates.

2. BACKGROUND

There are a number of licences held for this active constituent, including the brand leader Konakion 10mg tablets (PL 00031/5022) which was granted a reviewed licence in December 1985.

The Applicants, Bio-medical Services Ltd., are requesting a licence for this presentation for use in neonates as prophylaxis against Haemolytic Disease of the Newborn.

3. INDICATION

Prevention of vitamin K deficiency bleeding in babies

4. DOSE & DOSAGE SCHEDULE

Oral prophylaxis in healthy neonates, including healthy preterm babies:

The contents of a single Neokay capsule should be administered by cutting the narrow tubular tip off the capsule and squeezing the liquid into the baby's mouth. Another dose should be given if the first dose is spat out or the baby is sick within three hours of the dose being given.

Unwell babies and babies of mothers taking carbamazepine, phenobarbital, phenytoin, rifampicin or warfarin at the time of delivery:

Babies who are not well enough to be fed within a few hours of birth and babies whose mothers are taking any of the above drugs should be treated with an intramuscular formulation of vitamin K at birth.

Exclusively breast fed babies:

The administration of 1mg Neokay by mouth at birth protects healthy term babies from the risk of bleeding due to vitamin K deficiency in the first week of life. Evidence to date suggests that for babies who are being exclusively breast-fed, a dose of 1mg once weekly for 12 weeks offers the best protection against late vitamin K deficiency bleeding.

5. HUMAN PHARMACOLOGY

This product is a soft gelatine capsule containing 1mg of phytomenadione in an oil base. It is intended that the top of the capsule should be cut off before administration, squeezing the contents into the mouth of the neonate. Although the Applicants state paraenteral Konakion has been in widespread use, administered orally for the prophylaxis of HDN for many years, there is considerable discussion amongst clinicians as to whether there is adequate uptake of the active constituent, as it is known that bacterial activity is required to facilitate absorption from the gastrointestinal tract. Those against giving Vitamin K by the oral route have argued that there is inadequate bacterial colonisation of the neonatal gastrointestinal tract for adequate uptake to be able to occur.

No *in vivo* pharmacokinetic data has been presented with this application.

6. CLINICAL EXPERIENCE

No clinical data concerning this presentation has been submitted with application.

A review article by Handel and Tripp “On the use of Vitamin K prophylaxis against Haemorrhagic Disease in the Newborn” includes a survey of current usage of oral and intramuscular prophylaxis on neonates units in the UK. This suggests that 65 out of 255 units surveyed (25%) were routinely using oral Vitamin K prophylaxis with parenteral administration in selected cases while 2 units (1%) were using solely oral administrations for all babies.

7. EXPERT REPORT

The clinical expert report has been written by suitably qualified person and is satisfactory.

8. PHARMACOVIGILANCE SYSTEM

The pharmacovigilance system as describes by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring whether in the Community or in a third country.

9. PRODUCT LITERATURE

9.1 Summary of Product Characteristics (SmPC)

The SmPC was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisation.

9.2 Labelling

Labelling was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisation.

9.3 PIL

The PIL was assessed and amended and found to be satisfactory at the time of grant of the Marketing Authorisation.

10 CLINICAL CONCLUSION

In the absence of adequate evidence of efficacy, a licence should not be granted.

In additional the clinical assessor requested changes to the SmPC and product literature; a satisfactory SmPC and PIL were arrived at during the assessment process.

COMMITTEE ON SAFETY OF MEDICINES RECOMMENDATIONS AND ASSESSMENTS OF APPLICANT RESPONSES

The application was considered by the Commission on Human Medicines (CSM) on 3rd December 1991, 23rd July 1998 and an Appeal Hearing on 8th February 2002. The information contained in this part of the Public Assessment Report concentrates on the resolution of major issues which led to the granting of the Marketing Authorisation.

1.1.1.1.1 1 INTRODUCTION

This is an appeal by Bio-Medical Services Limited to the Medicines Commission for Neokay (phytomenadione, vitamin K) 1 mg in 1ml of fractionated coconut oil for the indication prophylaxis by mouth to prevent haemorrhagic disease of the newborn.

1.1.1.1.2 1.1 NEOKAY

Neokay is a soft gelatin capsule containing 1mg of vitamin K₁ in 1ml of a fractionated coconut oil base. It is administered by cutting open the capsule and dropping the liquid directly into the mouth. The company is seeking an indication for the prophylaxis of Haemorrhagic Disease of the Newborn (ie early bleeding).

1.2 VITAMIN K DEFICIENCY BLEEDING (previously termed Haemorrhagic Disease of the Newborn)

Vitamin K deficiency bleeding (VKDB) was described over 100 years ago and was then termed haemorrhagic disease of the newborn (HDN). An Expert Committee convened by the Department of Health in July 1992 to advise on the administration of vitamin K agreed that the term 'Haemorrhagic Disease of the Newborn' was potentially misleading – it did not mention vitamin K or exclude other causes of bleeding and it erroneously implied a condition confined to the newborn period. VKDB is now the preferred phrase.

Classical VKDB is used to describe bleeding in the 1st week of life (Classic VKDB). Late onset VKDB (late VKDB) is rarer and has a higher morbidity and mortality rate. Classical VKDB has been recognised for over 50 years. It presents with bleeding from the umbilical stump, gums, bowel or with excessive bleeding after venepuncture or after surgery. Incidence rates before the introduction of prophylaxis of 2 – 17 per 1000 births have been quoted (Lane, Hathaway, Vitamin K in Infancy, *Journal of Pediatrics* 1985;106(3):351-359). The rates depend on feeding practices as even small amounts of formula feeds which are supplemented with vitamin K may be protective. Late VKDB presents in the 7 day to 6 month age period, often with cerebral bleeding. Various series have found that about 50-60% of those affected by late VKDB die or are left with severe and permanent brain damage (Loughan PM, McDougall PN. Epidemiology of late onset haemorrhagic disease. A pooled data analysis. *J Paediatr Child Health* 1993;29:177-81, Cornelissen et al. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. *Eur J Pediatr* 1997;156:126-30). The diagnosis includes two groups of infants, those in whom there is an underlying cause, usually liver disease and those in whom there is

no secondary cause for the vitamin K deficiency. It is more helpful to classify the disorder as vitamin K deficiency bleeding, early form (0-1 day), classic form (2-7 days) and late form (8 days- 6 months). A more recently internationally adopted definition of VKDB is any infant under 6 months of age with spontaneous bruising/bleeding or intracranial haemorrhage associated with prolonged clotting times, not due to an inherited coagulopathy or disseminated intravascular coagulation.

The company has used the term HDN in its written documentation to describe 'early' bleeding between the 2nd and 7th day of life and subsequent vitamin K deficiency bleeding as late VKDB.

Examiners' comments

It is confusing to use the term HDN without specifying the age. Although the company has defined the terms HDN and late VKDB in their appeal documentation, the proposed SPC refers to HDN which is potentially misleading and confusing to the prescriber. However this is also used in the SPC for Konakion, a licensed product.

Vitamin K1 is also known as phylloquinone and is synthesised naturally by plants. Phylloquinone is fat-soluble and the manufactured product used for intramuscular injection is 'solubilised' using a polyethoxylated castor oil. This formulation has the name phytomenadione.

1.1.2 CURRENT MARKETING AUTHORISATIONS FOR VITAMIN K FOR USE IN NEONATES

MA Holder	Licensed Name	Posology	Date authorised
Roche Products Ltd	Konakion Ampoules 1 mg/0.5 ml	Intramuscular prophylaxis of haemorrhagic disease of healthy neonates of 36 weeks and older	July 1985
Roche Products Ltd	Konakion MM Paediatric 2 mg/0.2 ml	Prophylaxis and treatment of haemorrhagic disease of the newborn Oral for healthy neonates of 35 weeks gestation and older IM or IV for preterm neonates of less than 36 weeks gestation	June 1996

1.1.2.1.1 1.3 RECENT ISSUES SURROUNDING ADMINISTRATION OF VITAMIN K

Intramuscular (IM) vitamin K will prevent VKDB in virtually all babies given a single dose at birth. It became routine practice to give intramuscular injection from the 1960's. Oral vitamin K has been shown to be effective but repeated doses need to be given for it to be as effective as intramuscular vitamin K presumably because of more rapid gut absorption. Formula fed babies continue to receive vitamin K in their milk as formula milk is supplemented with vitamin K. A second dose of oral vitamin K is still advisable for formula fed babies to make up for any failure to absorb the dose given at birth. Exclusively breast fed babies should be given further doses. Late VKDB is more common in exclusively breast fed babies. There is no doubt that

vitamin K, orally or IM prevents the early and classic forms of VKDB. Surveys have shown that only in very exceptional circumstances do infants who have been given IM vitamin K develop VKDB (early or late) but it is not certain why the IM preparation is more effective than a single dose of oral vitamin K, but this is likely to be because of a depot effect. Vitamin K is fat soluble so a depot effect is compatible with this fact. It is also relevant to the problems of children with liver problems resulting in fat malabsorption.

In 1990 and 1992, Golding *et al* published papers suggesting an association between IM vitamin K and the development of cancer in childhood. The CSM reviewed the issue firstly in 1990 and twice in 1992. In 1992 they concluded that the studies up to then did not provide substantive evidence that IM vitamin K given to the newborn posed a carcinogenic risk. If IM vitamin K does cause cancer, the mechanism is not known. Various suggestions have been made, but no convincing evidence has been given for any of them. Other studies carried out internationally did not confirm the findings of Golding. The amount of data available for oral administration did not allow for a clear distinction between it and no use or between it and IM use.

In the light of this uncertainty, a number of UK studies were set up and in 1996 and 1997, these were completed and published. A Vitamin K Working Group of the CSM was set up and met in September 1997. The Working Group concluded that there was no evidence to suggest that there was an association between IM Vitamin K administration and development of solid tumours in children. There were fewer data for leukaemia, the findings of the epidemiological studies were inconsistent and a relatively small increased risk in the development of leukaemia could not be excluded. The Working Group considered that the efficacy of 1mg IM Konakion was well-established in the prevention of vitamin K deficiency bleeding. The formal conclusions of the Working Group were summarised in the MCA/CSM bulletin for health professionals, Current Problems in Pharmacovigilance.

In order to attempt to clarify the somewhat differing conclusions of the differing studies, the Department of Health Research Division funded a study to amalgamate data from the individual studies (an individual patient data meta-analysis). The conclusion is that there is little support for the suggestion that IM neonatal vitamin K influences cancer risk. However one of the groups of investigators who provided data and whose studies suggested such a risk, have raised objections to the final paper. They were unhappy with the changes requested by the referees and editors of the journal. In view of the controversy over this proposed publication, a paper was prepared for the Working Group on Paediatric Medicines (a CSM Working Group) at their February 2001 meeting. This Group has paediatric expertise and this meant there was no need to reconvene the Vitamin K Working Party. The Working Group concluded that the new paper had not changed the 1997 conclusions of the Vitamin K Working Party. They were unanimous in the view that the current evidence did not indicate a substantial risk of childhood cancer and the results of the Bristol study had not been confirmed.

1.1.3 1.4 CURRENT POSITION

There are a number of factors to be taken into account by health professionals when deciding the route of administration of vitamin K. Anxieties (by parents and

paediatricians) surrounding the publications suggesting a link between IM vitamin K and childhood cancer has led to a trend in prophylaxis of vitamin K deficiency bleeding using oral preparations. In addition it is thought to be preferable not to give every newborn infant an IM injection at birth, particularly as it introduces a potential for error in administering the wrong drug. However until recently there has not been a licensed oral vitamin K preparation and a number of health professionals, expressed concern over giving vitamin K either off-label or in an unlicensed formulation. It had been the practice in many units to give the product licensed for IM use orally. There is now a product licensed for use orally, but this is still given at relatively high doses. It is called a "Mixed Micelles" form that is colloidal. The main purpose of its introduction was to prevent the anaphylaxis that can occur with the original formulation. Anaphylaxis does not occur in the newborn and is very rare in children under one year of age, but it does occur in adults and the original Konakion is also used to prevent bleeding in adults. It is important to note that although IM vitamin K appears to protect against both early and late VKDB, a single dose of the oral preparation may not protect against late bleeding.

In 1996 a marketing authorisation was granted for the vitamin K preparation Konakion MM Paediatric, 2 mg/0.2 ml (Roche). Oral dosing was authorised for the prophylaxis and treatment of haemorrhagic disease of the newborn. The dose for healthy neonates of 36 weeks gestation and older is 2 mg at birth and 2 mg at 4-7 days. A further 2mg should be given to exclusively breast fed babies at one month after birth and 2mg monthly is advised until formula feeding is introduced. Oral dosing is not indicated for pre-term infants, only IM or intravenous use.

1.5 CURRENT DEPARTMENT OF HEALTH ADVICE

The current advice is that 'all newborn babies should receive an appropriate vitamin K regime to prevent the rare but serious and sometimes fatal disorder of VKDB. All should be offered one of the available regimes after an informed discussion with parents in the antenatal period.' The advice recommends that vitamin K should be given by IM injection or using an oral regime. It states that an oral preparation is available in the form of Konakion MM (Roche) and is licensed for oral use in two doses of 2 mg to be given in the first week for all babies and for exclusively breast fed babies a third dose of 2 mg is to be given at one month of age. This advice was issued in a letter from the Chief Medical Officer in 1998.

2 2 BRITISH PAEDIATRIC SURVEILLANCE UNIT STUDIES

The British Paediatric Surveillance Unit, part of the Research Division of the Royal College of Paediatrics and Child Health, has completed two studies of vitamin K deficiency bleeding, the first in 1989-90 and the second in 1993-4. These studies are prospective surveillance studies. The first was published by McNinch and Tripp in the British Medical Journal in 1991. In the first study, 27 infants were classified as having confirmed or probable haemorrhagic disease of the newborn among 1,671,000 live births, a rate of 1.62 per 100,000 births. The authors calculated that the relative risk was 81.7 in babies given no prophylaxis, 13.4 in babies given oral prophylaxis, 5.75 in babies without liver disease given oral prophylaxis and 1.0 in babies given IM prophylaxis. A distinction between the risks of early or late bleeding was not made by the authors.

The second study has not been published in a peer-reviewed journal.

2.1 Vitamin K Deficiency Bleeding in the British Isles, 1993-94: Second National Survey. McNinch & Tripp [unpublished]

This covers all births in the two years in the United Kingdom and in Eire. There were 1.6 million births in those years and there were 30 confirmed and 2 probable cases of VKDB.

Route and dose of vitamin K prophylaxis:

Most (20) bled after oral administration, 10 with no VK prophylaxis and two after IM VK (one after the licensed dose of 1mg, and one with the BPA recommended dose of 0.1 mg). Sixteen of those with oral doses received a single dose; two received two doses and two had three doses. Most of the oral doses were of 1mg. Twenty five of the babies were solely breast fed, and three were formula fed (two of them with soy milk).

Age at onset of bleeding:

Three babies bled within 24 hours (one prior to any feed) - "early VKDB"; three bled between 24 hours and 7 days "classical VKDB", and 26 were "late VKDB".

It seems that the early and classical cases received no prophylaxis (though it is possible one might have received it).

Other factors: Nearly half the babies had minor bleeds at least one day before presentation, and about half those whose liver function was tested (the majority) had liver disease or abnormal liver function tests.

As these two BPSU surveys showed that VKDB was still occurring in the British Isles despite widespread use of vitamin K prophylaxis and in view of the varying regimens (no routine prophylaxis, single oral dose, multiple oral doses, IM), a third BPSU study was started in January 2001. To date there have been 6 confirmed cases of VKDB, of which 2 cases were less than 7 days. Since 6 August 2001 there have been 6 further

cases. The BPSU office has provided these data, though no information is available on vitamin K prophylaxis.

2.1.1.1 SUMMARY OF REGULATORY HISTORY OF NEOKAY

1989 - Abridged product licence application submitted.

1991 - CSM considered application and advised that on grounds relating to efficacy that they would be unable to advise that a Marketing Authorisation should be granted

1998 - Hearing requested and considered by CSM. The Committee advised the Licensing Authority not to grant a marketing authorisation for this product. The detailed reasons for this are given below.

3 3.1 SUMMARY OF ISSUES CONSIDERED BY CSM AND CSM ADVICE

1991 - Application considered by CSM. The Committee had reason to think that on grounds relating to efficacy, they would be unable to advise that the Marketing Authorisation applied for should be granted. The Committee provisionally concluded that:

1. There was inadequate evidence of efficacy in the prophylaxis of Haemorrhagic Disease of the Newborn
2. The Summary of Product Characteristics (SmPC) should be amended to the satisfaction of the Secretariat, in particular the treatment of haemorrhage or threatened haemorrhage should be deleted from the Indications section

1998 - The company requested a hearing by the CSM and submitted further data. The Hearing was held in July 1998.

After a number of pharmaceutical concerns were resolved between 1989 and 1991, in 1991 Neokay was considered to be of satisfactory quality. By 1998, the pharmaceutical issues needed updating and at the time it was considered that a marketing authorisation could be granted provided 5 points were resolved. These were:

1. European Marketing Authorisation Application Form duly completed is required.
2. Acceptable Summary of Product Characteristics is required.
3. Information is required on product packaging, labelling and Patient Information Leaflet in line with Directive 92/27/EEC
4. The source of active should be restricted to the named source, known to the Licensing Authority. Compliance is required with a Ph.Eur monograph on phytomenadione.
5. The manufacturing process, in-process controls, the finished product specification and analytical methods should be updated in line with the current CPMP guidelines.

With respect to the Committee concerns over efficacy, (letter dated 3 December 1991 to Applicant, point 1) the company submitted 3 reports:

1. A Company survey of hospitals using Neokay
2. The manuscript of a letter to the BMJ relating to the Northern Neonatal Network Study (BMJ 1998; 326:230).
3. A report of a bioavailability study undertaken in Sheffield.

The company survey of hospitals using Neokay was only briefly reported and no formal report was presented. Clinicians in each of the hospitals supplied with Neokay were asked if they knew of any cases of VKDB which had occurred between the date on which it had been first supplied and end December 1996. 120 hospitals were approached, 8 were excluded from the analysis and 101 complete responses were obtained. 14 possible cases of haemorrhage were reported. The company used a denominator of 310,204 neonates treated and reported an incidence of 3.2 per 100,000. This excluded 4 cases.

Examiners' comments:

Few details on how the denominator was calculated were given by the company. Similarly few details were given on whether the company was satisfied that they had identified all cases of VKDB cases.

The Northern Neonatal Network Study was a retrospective review. Hospitals in the north of England adopted a relatively uniform practice for vitamin K prophylaxis. IM vitamin K was only given to babies judged not well enough to be offered milk on the 1st day of life. The letter in the BMJ reported that during 1993-1996 only 3 cases of late bleeding were identified among the 147,271 babies delivered in the region. All were breast fed. This gave an incidence of 2 per 100,000 births.

Examiners' comments:

Again few details were provided on this study (the letter published in the BMJ was submitted) : in particular details of how the denominator was determined, how the cases were identified and how the authors ensured that collection of cases was complete were missing

A pre-publication report of a bioavailability study conducted at the Northern General Hospital in Sheffield was submitted for the CSM appeal. 55 preterm infants admitted to the Special Care Baby were studied. Infants were given either Neokay (n=21), Konakion (n=9) or Konakion MM (n=9). Circulating vitamin K levels were measured at 4, 24, and 48 hours after dosing. The vitamin K levels were widely inconsistent for each of the formulations. Circulating vitamin K was significantly higher after the intravenous formulation than the oral formulations at all 3 time points. The company stated that the minimum dose of vitamin K necessary to prevent VKDB is not known nor is the precise mechanism by which a single IM dose of vitamin K protects against late onset VKDB known. They concluded that as the levels of vitamin K after Neokay were considerable higher than those in mature adults, this should be sufficient to protect against haemorrhage.

Examiners' comments:

The company has not made it clear that this bioavailability study was not intended to be a bioequivalence study. The results of this study showed a wide variation in blood levels of vitamin K for each of the formulations. It is difficult to make any meaningful

interpretation of this study because it is not known what serum levels of vitamin K are required to prevent VKDB. The relationship between blood levels and body stores is also not known.

The main points of concern by the Committee which were discussed after the company presentation are listed below:

1. The Committee were concerned that the kinetic study did not show evidence of bioequivalence and that 50% of babies receiving Neokay had low levels of vitamin K.
2. The Committee were concerned that it is difficult to show protection using the study approaches taken by the company.
3. The Committee were concerned that the company survey was not a reliable method of identifying cases.
4. The Committee were concerned that the Northern survey was not prospective.
5. The Committee were concerned about the widespread use of a product which was not currently authorised as a medicinal product.

In summary, the Committee were not reassured by the company's oral presentation on points 1 and 2 raised in 1991. It advised the Licensing Authority not to grant a marketing authorisation for this product. The reasons were:

1. The Committee were not reassured regarding the evidence of efficacy in the prophylaxis of Haemorrhagic Disease of the Newborn. The Committee considered that the evidence of efficacy was still inadequate.
2. The Committee were not reassured that the proposed SmPC was adequate.
3. The Committee expressed concern that a substantial percentage of babies who received Neokay in the kinetic study had low vitamin K levels.
4. The Committee expressed concern that the case surveys presented were not adequately reliable methods to identify all cases of haemorrhagic disease of the newborn in patients given Neokay.
5. The Committee expressed concern that the case surveys presented by the company were not adequately reliable methods to determine the incidence of haemorrhagic disease of the newborn in patients given Neokay.

4 APPEAL TO MEDICINES COMMISSION:

Summary of new data

For their appeal, the company has submitted :

1. An extension of the company survey to include 1997 and 1998
2. The publication of the Northern Neonatal Network study which includes more details of the methods of this study and an update of this study up to the end of 2000 (Appendix VI of Appeal document)
3. The results of a cross-validation of these two studies with an independent study by BPSU undertaken in 1993 and 1994

The company has submitted an appeal against the CSM advice of 1998 to the Licensing Authority. This is bound separately as Document 3 and consists of two

volumes; the first is the appeal and the second is a set of references that have been quoted by the company in their appeal.

4.1 ASSESSMENT OF WRITTEN REPRESENTATION

The Northern Neonatal Network Study has been published since the CSM Hearing and the Company Survey has been extended to include 1997 and 1998. Both studies have been cross-validated (by matching individual cases) with the 1993-4 BPSU study of VKDB by McNinch and Tripp. The written representation by the company rests on one pivotal point: the company submits that the failure of 3 separate surveys to identify a single case of haemorrhagic disease of the newborn (NB early bleeding) over a period of 8 and a half years despite usage in more than 700,000 babies provides acceptable evidence of efficacy.

The company acknowledges that evidence of efficacy in the original 1991 application relied on the accepted use of vitamin K prophylaxis and that direct evidence was not submitted. They defend this by saying that placebo-controlled trials would have been unethical and a conventional double-blind parallel study against the licensed IM preparation would have been impractical because of the very large sample size required. Each of the CSM's 5 concerns is addressed in the representation to Medicines Commission.

Point 4:

The Committee expressed concern that the case surveys presented were not adequately reliable methods to identify all cases of haemorrhagic disease of the newborn in patients given Neokay.

The Company have defended the two surveys (Company Survey and Northern Neonatal Network Study) by validating the results of both with the BPSU 1993-1994 study, see above. This study was an independent prospective nationwide surveillance study. The BPSU is part of the Royal College of Paediatrics and Child Health, Research Division and enables paediatricians to participate in the nationwide surveillance of infections and infection-related conditions, to promote the study of uncommon childhood disorders, and to provide a mechanism by which 'new' diseases can be detected so that early investigation can take place. BPSU operates an active surveillance clinical reporting mechanism. As such it elicits monthly reports from nearly all hospital, university and community consultant paediatricians seeing child patients in the United Kingdom and the Republic of Ireland. When a patient with one of the conditions under study is reported, the Unit passes this information on to a research worker for investigation. The methodology of BPSU studies of rare paediatric disorders is well-established and the response rate of paediatricians is over 90%. The cross-validation of individual cases from the two surveys with the BPSU 1993-1994 study was remarkably consistent.

Company Survey:

The BPSU detected 2 cases of late VKDB not known to the Company and the Company identified 2 cases of late VKDB not known to BPSU.

Cross-validation of the Company survey with the Northern Neonatal Network Study confirmed that the same 3 cases of late VKDB in the Northern Region had been detected by each study. This cross-validation was done by the author of the 1993-

1994 BPSU study using their database to cross-check names and dates of birth. The Company state that there were no reported cases of HDN (early bleeding) in any of the 3 surveys. Their extended survey since the 1998 hearing includes the years 1997 and 1998 when 2 more cases of late VKDB were identified. They are now aware of 13 cases of late VKDB over a 6 year period. Of the original 14 cases in the Hearing document, 5 have been omitted (2 after discussion between an independent paediatrician and the reporter and 3 are counted in the Northern Neonatal Network study), 2 identified by the BPSU study have been added and the 2 new cases have been added (a total of 13 cases).

Northern Neonatal Network Study:

This study identified a total of 4 breastfed babies who developed late VKDB and no cases of early VKDB (Appendix IV of Company appeal document). Of the 4 who developed late VKDB, one had not received any prophylaxis and two were later found to have alpha-1 antitrypsin deficiency. The 4th baby received only a single prophylactic dose of oral vitamin K and was admitted with blood streaked vomiting at 46 days. These cases were validated against the BPSU study of 1993-94 and no discrepancies were found.

At the time of the appeal to CSM there was concern that, as only the letter to the BMJ on this study was submitted, the data provided were lacking in details such as an explicit statement that ‘there were no classic cases of VKDB’ and that the oral preparation used was actually Neokay. The company have acknowledged this but state that this was the only information available to them at the time. The results of this study have been extended to include the years 1993-1998 and have been published in Archives of Disease in Childhood (Wariyar et al, 1999, Appendix IV, Company appeal document).

Examiners’ comments

It is certainly reassuring that the company has validated the results of both the Company Survey and the Northern Neonatal Network Study with a BPSU study. The results of these 3 studies are consistent. It is not clear that any more valid methods of ascertainment would result in higher estimated rates of VKDB.

Point 5

The Committee expressed concern that the case surveys presented by the company were not adequately reliable methods to determine the incidence of haemorrhagic disease of the newborn in patients given Neokay.

The company has used incidence as the number of children with HDN (that is early VKDB) divided by the estimated number of children treated.

Company Survey:

At the time of the appeal to CSM there was concern that the company had not made it clear how the denominator had been calculated (number of doses supplied or number of babies treated). In the current appeal documentation, the company has clarified their calculations. The total number of 310,204 babies reported in the Hearing to CSM included those in the Northern Region and was reached by counting the number of names held on file by the Company and names held on file by Pharmacies who, for confidentiality reasons, would not release names. Thirty hospital pharmacies

calculated a number in the event that the list of names had been archived (115,551, 37%, of the 310,204 babies).

Northern Neonatal Network Study:

The company accepts that the letter to the BMJ did not give details of the proportion of babies who received IM vitamin K and also did not state how their denominator had been derived. These details are provided in the full publication. A total of 193,472 babies were born in the study units. About 6% of the 193,472 babies were given IM prophylaxis (estimated from an audit of 1400 case notes) to leave a denominator of 182,000 babies given Neokay. The full publication also makes it clear that the oral preparation was Neokay, not another preparation.

Examiners' Comments

In the company survey, 1992-1996, details of how the hospital pharmacies calculated the number of babies given Neokay are not provided. This number amounts to 37% of the total denominator of 310,204. It is not possible to be sure whether this is an overestimate or underestimate. The numbers of children who had formula feeding should be subtracted from the denominator as they are not at risk of VKDB because of their supplementation with vitamin K.

Point 1

The Committee were not reassured regarding the evidence of efficacy in the prophylaxis of Haemorrhagic Disease of the Newborn. The Committee considered that the evidence of efficacy was still inadequate.

The company believe that the only practical way to show efficacy of Neokay is to review the available evidence regarding its use in clinical practice. The company have estimated that at least 700,000 babies have received Neokay prophylaxis and there has not been a single case of early VKDB (referred to as HDN by company). Also 11 of the 17 cases of late VKDB resulted from a failure or provide what would now be considered optimal post-discharge booster prophylaxis to those breast fed babies who were given oral prophylaxis.

Company Survey:

The overall number of capsules supplied by the company is 1,813,148 between May 1992 and December 2000. The company have estimated the number of babies treated using the assumptions that most bottle-fed babies were given a single dose, 70% of babies were initially breast fed and that breast fed babies were given an average of 4 doses. They have derived an estimate of a minimum of 459,951 babies given prophylactic Neokay in hospitals outside the Northern Region between May 1992 and December 1998 and 584,886 between May 1992 and December 2000. This usage is despite the fact that Neokay is an unlicensed preparation.

Incidence of early VKDB (HDN)

The company submit that the absence of a single case of early VKDB over an 8 year period shows the product to be as efficacious as other products in use in Europe and the UK. They defend the argument that they might not have identified every case with the argument that their audit of cases was as thorough as other audits in Europe and Australia during the same period of time.

Late VKDB

The update number of cases of late bleeding, 13 among 459,951 babies treated gives a maximum incidence of 2.8 per 100,000 births. The company states that this is an acceptable incidence when compared with other studies.. This incidence is higher than in most of the studies that used repeated oral dosing of vitamin K and is certainly higher than the incidence of late VKDB after IM vitamin K. However accurate details of the number of doses of Neokay given to babies is not provided in the documentation of the company survey.

Northern Neonatal Network Study

Two authors of this study have provided an update of their study up to the end of 2000. There has not been a single case of early VKDB among 254,000 babies given a single dose of Neokay at birth. In this study, breast fed babies were given a further 3 doses at fortnightly intervals (ie a total of four 1 mg doses). Four cases of late VKDB were identified although one of these had received only one dose, 3 cases in those given fortnightly prophylaxis, an incidence of 1.2 cases per 100,000 babies treated. The overall pattern of results is similar, but there are increases in the updated rates of late VKDB from both UK and German studies, particularly for those with no prophylaxis.

Examiners' comments

This is the key argument of this appeal- that the absence of a single case of early VKDB (HDN) in over 8 years usage is evidence of the efficacy of Neokay. The high level of unlicensed usage and the absence of reported cases is certainly reassuring evidence of its efficacy. It could be argued that because of the unlicensed use, not all cases might have been reported but the cross-validation with the BPSU study is consistent. It is also important to note that the company are seeking authorisation for the prevention of early VKDB.

Compared with no prophylaxis, it does seem that oral regimens in general reduce the incidence of VKDB, and that early (0-6 days) VKDB has a very low (0/254,000) incidence if oral administration occurs. An independent review of the data, written from the perspective of paediatricians from Newcastle has been presented by the Applicant. The regimen used in Newcastle of three further 1 mg doses at fortnightly intervals also seems to have shown a reduced rate of late bleeding. However, the denominators for the rates have not been adjusted for the numbers of children given formula feeds (which may be quite high for those given IM vitamin K (a rather small number).

The evidence presented suggests that Neokay does not prevent all cases of late bleeding unless dosing is repeated and even then prevention is not 100%.

Point 3

The Committee expressed concern that a substantial percentage of babies who received Neokay in the kinetic study had low vitamin K levels.

In response to this point, the company states that the serum vitamin K levels in all but one of the 58 measurements obtained from pre-term infants 4, 24 and 48 hours after birth were within or above the normal adult range of 0.1 – 0.8 ng/ml, therefore ‘there is no scientific basis to justify the statement that vitamin K levels were low in a substantial percentage of babies’.

Examiners' comments

There are no new bioavailability data. The results of the previous bioavailability study showed widely varying serum vitamin K levels between the different preparations and it appeared that the levels of Neokay were lower than the other preparations. However dose ranging studies have not been submitted and it is not known what dose of vitamin K or what serum levels are required to prevent VKDB, early or late. In addition interpretation of serum levels is complicated by vitamin K body stores. In this respect, this bioavailability study adds little to help in assessing the efficacy of Neokay given the large volume of clinical data.

SUMMARY OF FINDINGS

Point 1: The Committee were not reassured regarding the evidence of efficacy in the prophylaxis of Haemorrhagic Disease of the Newborn. The Committee considered that the evidence of efficacy was still inadequate.

Medicines Commission was satisfied that the applicant had shown adequate evidence of efficacy by the three surveys.

- Point 2: The Committee were not reassured that the proposed Summary of Product Characteristics (SmPC) was adequate.

Medicines Commission advised that the SPC had minor deficiencies and its exact wording should be drafted by the secretariat.

- Point 3: The Committee expressed concern that a substantial percentage of babies who received Neokay in the kinetic study had low vitamin K levels.

Medicines Commission concluded that the bioavailability data were not helpful as they were difficult to interpret. In the presence of evidence of clinical efficacy in very large numbers; bioavailability data were not relevant. The Commission also took the view, supported by the experts, that the low levels of vitamin K seen in the study submitted by the company, about which CSM had concerns, were no different to levels seen in other studies.

- Point 4: The Committee expressed concern that the case surveys presented were not adequately reliable methods to identify all cases of haemorrhagic disease of the newborn in patients given Neokay.

- Point 5: The Committee expressed concern that the case surveys presented by the company were not adequately reliable methods to determine the incidence of haemorrhagic disease of the newborn in patients given Neokay. The Medicines Commission were satisfied with the methodology of the surveys and that the estimates of numerator (number of cases of haemorrhagic disease of the newborn) and denominator (usage) were the best possible estimates that could be obtained. The validation of cases between the company survey and the British Paediatric Surveillance Unit survey showed good concordance.

4.2 PHARMACEUTICAL ASSESSMENT

In 1998 it was concluded that the product quality was satisfactory and it was recommended that a marketing authorisation could be granted provided that the 5 points stated earlier in this Public Assessment Report were resolved. The company submitted its response to these points on 18th January 2002. In summary:

- The European Marketing Authorisation Application Form has been signed and submitted.
- A revised SmPC was submitted.
- Mock-ups of the labelling and the Patient Information Leaflet were submitted.
- The source of the active will be restricted.
- The manufacturing process, in-process controls, the finished product specification and analytical methods have been updated in line with the current CPMP guidelines.

This application was received on 28 November 1989. The last assessment of this application was seen by CSM at a meeting of 23 July 1998. The refusal was on grounds relating to efficacy. There were no scientific quality points remaining outstanding at that time. However, the company was informed that the updating of regulatory and pharmaceutical issues would be required for all products particulars for this product as a considerable time has lapsed since this application was first received and assessed. This is necessary as the regulatory requirements have changed over the last 10 years.

5 OTHER RELEVANT DATA

The general scientific consensus is that there is good evidence that oral regimens do reduce incidence of VKDB compared with no prophylaxis. The best review of which the examiners are aware is that carried out for the Department of Health by Logan and Gilbert of the Institute of Child Health, Systematic reviews Unit.

This sets out the general background of the history, risk factors and outcome of VKDB (though it refers to Haemorrhagic Disease of the Newborn – HDN-consistently).

In discussing the natural history of VKDB it states:

“Where the aim is to assess the impact of different forms of vitamin K prophylaxis it is important to consider both classic and late cases as the aim of prophylaxis is to prevent all types of vitamin K deficiency bleeding.”

A complete literature survey was carried out and an attempt was made to estimate rates of VKDB under various regimens, paying particular attention to oral administration.

Since VKDB occurs almost exclusively in breast-fed babies, the authors made a good attempt to estimate the true population at risk of VKDB, by subtracting those who were formula-fed where possible. When oral regimens were studied, they also attempted to remove those who were given IM vitamin K; they did not allow for the

fact that since these were presumably high risk anyway, that the rates in those who did not have IM administration would be expected to be lower. However, with the exception of overt liver disease, the predictive power of “high risk” for VKDB is not very great.

They also attempted to allow for compliance with different regimens, but note that these may not be well estimated and that serious bias is possible in the estimated rates.

They estimate that the rate of VKDB (as a whole) is 10-15 per 100,000 breast fed infants. They state “the results summarised here suggest that all proposed regimens for vitamin K prophylaxis will prevent a substantial proportion of ... cases.”

They state that “There is no evidence from this data that giving 3 or 4 doses of oral vitamin K is more effective than a single dose”. They note that they would expect multiple doses to be more effective on theoretical grounds, but the events are so rare that detecting a difference between regimens is very difficult indeed.

They do suggest that repeated weekly or daily doses appear to offer greater protection and that a single 1mg IM dose will prevent virtually all cases of VKDB. They note the problems of compliance with the use of this route.

The key values (which have notable uncertainty in spite of studying hundreds of thousands or even millions of births) are:-

Vitamin K prophylaxis	Incidence of VKDB/100,000 breast fed babies
None	12.5 (range 10-15)
1-3 doses given orally	3.6 (range 2.7-4.6)
Daily or weekly low dose	1.0 (range 0-2)
IM	0.1 (range 0-1.5)

The unpublished manuscript by McNinch and Tripp also emphasises the problems of compliance. The review paper by the same authors emphasises that confidence has been lost in the IM regimen and that compliance with this effective method of prevention is always going to be difficult. It is clear that even a small relative risk of leukaemia (around 1.5 or less) would outweigh the numerical risk of VKDB, though obviously the consequences of late VKDB are often catastrophic for a child.

6 EXAMINERS' SUMMARY

Early and late VKDB are rare but serious causes of morbidity and mortality, which are potentially preventable. The risk of late VKDB without prophylaxis varies from 3–7 per 100,000 births and a much higher figure for breast-fed babies. Oral regimens seem to reduce this risk. The main questions of principle for Commissioners are-

- 1 Whether cases of VKDB (classic or late) have been missed by the surveys that are relied upon by the company.
- 2 Whether the children in these surveys have actually received Neokay.

- 3 Whether the data presented by the company of usage in more than 700,000 babies, is convincing evidence of efficacy of Neokay.

It is important to note that the company is seeking authorisation for prevention of what they term HDN, early VKDB, not VKDB per se which encompasses both early and late bleeding. Commissioners should note that Konakion MM (Roche) is authorised for prophylaxis and treatment of haemorrhagic disease of the newborn. The SmPC for Konakion MM does not distinguish whether this refers to early, late or both early and late bleeding. The Konakion MM SmPC recommends that it should be given IM in preterm infants.

Medicines Commission may consider that a single oral dose appears to be efficacious in the prevention of VKDB bleeding in the first week of life. Multiple doses may reduce the risk of late bleeding but the optimum regimen is not known. The dosing regimen given in the company survey is not known. Data from the Northern Neonatal Network Study suggests that the risk of late bleeding is reduced eight-fold by a regimen of 4 doses at fortnightly intervals. However this may not prevent cases of late bleeding if occult liver disease is present.

The main outstanding question of detail in regard to the wording of the SmPC is-

- Should the indication be for overall prevention of VKDB, or only for early VKDB?
- If for overall prevention, what subsequent dosing regimen should be recommended?

6.1 ADVICE SOUGHT

The Commission advised that a Marketing Authorisation for Neokay should be granted for prevention of vitamin K deficiency bleeding. They recommended that the wording of the SPC needed clarification. The key points were:

- The indication should refer to vitamin K deficiency bleeding not haemorrhagic disease of the newborn.
- A single dose was only effective for one week.
- Weekly dosing for breast fed babies was necessary to prevent late bleeding.

Reasons for advice

- The usual requirements were that pharmacokinetic data were available to show that the medicine had the desired effect on surrogate variables. In this instance, there was a very large amount of data from unlicensed usage but where the ultimate outcome of bleeding had rarely been observed. There was sufficient evidence that cases of bleeding had been prevented, both of early and late cases.
- There was evidence from the surveys and the cases of bleeding that occurred during them, that the effect of Neokay persisted for some days after administration of an oral dose. The pharmacokinetic data were unclear, but the clinical cases were generally at least 7 days after a dose. Hence, in breast fed babies it was likely that dosing at weekly intervals during the at-risk period would prevent most cases of bleeding.

- The surveys of bleeding had been conducted to high standard. There was more than one independent source of data so that validation of each survey was possible. The number of cases that would have occurred had Neokay not been effective was large, and even if a very few cases had been missed in the surveys, they provided sufficiently robust evidence to demonstrate efficacy and safety.
- There were no quality concerns that had not been resolved.

Conclusion

Risk/benefit:

The data presented confirm that the benefit/risk ratio for Phytomenadione in the treatment of vitamin K deficiency bleeding in babies is acceptable.

The Licensing Authority has taken the Commission's report into account in reaching its decision and it accepts the advice of the Medicines Commission.

A Marketing Authorisation for this product can be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Neokay 1mg Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Phytomenadione (Vitamin K) is a fat soluble vitamin and is mostly required in blood coagulation. Phytomenadione is used to treat vitamin K deficiency bleeding in babies. Any safety concerns arising from this application has been fully resolved.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with phytomenadione is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**NEOKAY 1MG CAPSULES
PL 04532/0012**

UKPAR

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 28 th November 1989.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 26 th March 1990.
3	Following assessment of the application the MHRA assessment reports were considered by the Committee on Safety of Medicines on 3rd December 1991, 23 rd July 1998 and an Appeal Hearing on 8 th February 2002.
4	A Marketing Authorisation was granted on 15 th February 2010.

**NEOKAY 1MG CAPSULES
PL 04532/0012**

UKPAR

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

NEOKAY 1MG CAPSULES

PL 04532/0012

UKPAR

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Neokay 1mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft gelatin capsule contains 1mg phytomenadione.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft

The dark brown soft capsule contains a clear, odourless pale yellow liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Neokay is indicated for the prevention of vitamin K deficiency bleeding in babies

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Oral prophylaxis in healthy neonates, including healthy preterm babies:

The contents of a single Neokay capsule should be administered by cutting the narrow tubular tip off the capsule and squeezing the liquid into the baby's mouth. Another dose should be given if the first dose is spat out or the baby is sick within three hours of the dose being given.

Unwell babies and babies of mothers taking carbamazepine, phenobarbital, phenytoin, rifampicin or warfarin at the time of delivery:

Babies who are not well enough to be fed within a few hours of birth and babies whose mothers are taking any of the above drugs should be treated with an intramuscular formulation of vitamin K at birth.

Exclusively breast fed babies:

The administration of 1mg Neokay by mouth at birth protects healthy term babies from the risk of bleeding due to vitamin K deficiency in the first week of life. Evidence to date suggests that for babies who are being exclusively breast-fed, a dose of 1mg once weekly for 12 weeks offers the best protection against late vitamin K deficiency bleeding.

4.3 CONTRAINDICATIONS

Do not give further doses of Neokay to any baby showing evidence of hypersensitivity to any of the constituents.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Take expert advice before giving Neokay to any baby with protein C or protein S deficiency currently on treatment with warfarin.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Vitamin K acts as an antidote to the anticoagulant drugs of the coumarin type therefore concomitant use is not recommended except in the treatment of warfarin overdosage. It is not an antidote to heparin.

4.6 PREGNANCY AND LACTATION

Not relevant

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not relevant

4.8 UNDESIRABLE EFFECTS

No adverse effects have been associated with oral administration

4.9 OVERDOSE

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Vitamin K, ATC code: B02 BA01

Vitamin K is an essential co-factor in the hepatic synthesis of prothrombin (factor II) and of several other blood clotting factors (factor VII, IX, X and the coagulation inhibitors protein C and protein S). Low levels at birth may lead to the development of a generalised bleeding tendency (haemorrhagic disease of the new born).

5.2 PHARMACOKINETIC PROPERTIES

Phytomenadione is a fat soluble vitamin which does not cross the placenta readily. There is relatively little in human milk. Cow's milk contains more, and infant formula milks are artificially fortified. The half life in plasma is 2-3 hours. Vitamin K is absorbed from the small intestine and taken up by the liver but is only stored in the body for relatively short periods of time. Intra-muscular administration of phytomenadione in an emulsion may aid retention by setting up a "depot" muscle store. Bile salts aid absorption. The mixture of short and medium chain triglycerides contained in the Neokay formulation is readily absorbed, even in the absence of biliary and pancreatic secretions. The drug is metabolised to more polar metabolites and excreted in the urine and bile as glucuronide and sulphate conjugates.

5.3 PRECLINICAL SAFETY DATA

Not applicable

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**

Fractionated coconut oil (containing at least 95 percent of saturated 8 and 10 carbon atom fatty acids).

The soft capsule shell consists of gelatin, glycerol, iron oxide red (E172), iron oxide black (E172) and purified water

6.2 INCOMPATIBILITIES

None known

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Do not freeze.

Store in the original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

Polypropylene plastic bottles with LDP/HDP blend caps.

Containers contain soft gelatin capsules with pack sizes of 12 or 100.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

BioMedical Services Ltd
3 The Grange
Flaxby
Knaresborough, N. Yorks.
HG5 0RJ

8 MARKETING AUTHORISATION NUMBER(S)

PL 04532/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/02/2010

10 DATE OF REVISION OF THE TEXT

15/02/2010

NEOKAY 1MG CAPSULES

PL 04532/0012

UKPAR

PATIENT INFORMATION LEAFLET

Package leaflet: Information for the user

NeoKay 1mg Capsules

Phytomenadione

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare professional.
- If you notice any side effects, please tell your doctor or healthcare professional.

In this leaflet:

1. What Neokay is and what it is used for
2. Before you use Neokay
3. How to use Neokay
4. Possible side effects
5. How to store Neokay
6. Further information

1. WHAT NEOKAY IS AND WHAT IT IS USED FOR

Neokay contains a synthetic vitamin K called phytomenadione. Vitamin K is essential in the body for blood to clot. Newborn babies can have too little Vitamin K and so may develop a serious, but rare condition that causes bleeding. Neokay is used to prevent your baby from developing a tendency to bleed due to a deficiency in vitamin K.

2. BEFORE YOU USE NEOKAY

Do not use Neokay:

- if your baby is showing any signs of an allergic reaction to Neokay or any of its ingredients (listed in section 6)
- if your baby is not well enough to be fed within a few hours of birth
- if the baby's mother is taking carbamazepine, phenobarbital, phenytoin, rifampicin or warfarin.

Take special care with Neokay:

- if your baby has protein C or protein S deficiency and/or is currently being given warfarin. Do not give Neokay to your baby unless specifically advised to do so by their consultant
- if your baby has a bleed (e.g. from the cord stump) or shows signs of bruising consult your doctor immediately.

3. HOW TO USE NEOKAY

Always use Neokay exactly as your doctor has told you. You should check with your doctor or healthcare professional if you are not sure.

Healthy newborn babies, including healthy premature babies:

- The contents of a single Neokay capsule should be given
- Cut the narrow tip off the capsule and squeeze the liquid into the baby's mouth, as shown in the picture overleaf.
- Another dose should be given if the first dose is spat out or the baby is sick within three hours of the dose being given.

Continued overleaf

**Breast-fed babies:**

- Breast milk contains relatively little vitamin K.
- The contents of a single Neokay capsule should be given soon after birth. This protects healthy babies from the risk of bleeding due to vitamin K deficiency in the first week of life.
- For babies who are **only** being breast-fed, the contents of a single capsule should be given once weekly for 12 weeks. This offers the best protection against late vitamin K deficiency bleeding.
- Each dose should be given as described above.

If you forget to give a dose, give one as soon as you remember and continue to give the remainder of the doses as directed.

If you have any further questions on the use of this product, ask your doctor or healthcare professional.

4. POSSIBLE SIDE EFFECTS

There are no known side effects from taking Neokay. If you do notice any side effects, please tell your doctor or healthcare professional.

5. HOW TO STORE NEOKAY

Do not store above 25°C. Do not freeze. Store in the original package

Keep out of the reach and sight of children.

Do not use Neokay after the expiry date which is stated on the bottle (EXP). The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your healthcare professional how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION**What Neokay contains**

- Each capsule contains 1mg of the active substance phytomenadione.
- The other ingredient is fractionated coconut oil

What Neokay looks like and contents of the pack

Neokay comes as a dark brown soft capsule containing a clear, odourless pale yellow liquid. It is packed in polypropylene plastic bottles with caps made from a blend of low and high density polypropylene. It is available in pack sizes of containing 12 or 100 soft gelatin capsules.

Marketing Authorisation Holder

Bio-Medical Services Ltd, 3 The Grange, Flaxby, Knaresborough HG5 0RJ

Manufacturer

M&A Pharmachem Ltd, Wigan Rd, Westhoughton BL5 2AL

This leaflet was last approved in 11/2009

NEOKAY 1MG CAPSULES
PL 04532/0012
UKPAR
LABELLING

Carton

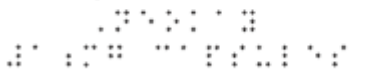
Each soft gelatin capsule contains 1mg Phytomenadione in fractionated coconut oil

Read the package leaflet before use
The contents of the capsule are to be given orally
Only for use in babies.
Keep out of the reach and sight of children
Store in a cool, dry place below 25°C
Store in the original packaging
PL04532/0012

Batch No.
Expiry Date.

POM

BioMedical Services Ltd 3, The Grange, Flaxby
Knaresborough, N. Yorks. HG5 0RJ

NeoKay[®]
1 mg capsules
Phytomenadione

12 capsules

Each soft gelatin capsule contains 1mg Phytomenadione in fractionated coconut oil

Read the package leaflet before use
The contents of the capsule are to be given orally
Only for use in babies.
Keep out of the reach and sight of children
Store in a cool, dry place below 25°C
Store in the original packaging
PL04532/0012

Batch No.
Expiry Date.

POM

BioMedical Services Ltd 3, The Grange, Flaxby
Knaresborough, N. Yorks. HG5 0RJ

NeoKay[®]
1 mg capsules
Phytomenadione

100 capsules