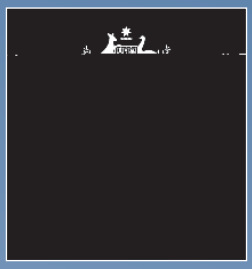

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Contents

Introduction

In December 1999 the Australian Drug Evaluation Committee approved the application by Roche Australia to register Konakion® MM Paediatric, which is the current formulation of vitamin K1 (phytomenadione) containing 2 mg in 0.2 mL, for intramuscular (IM) and oral use. In this mixed micelles formulation naturally occurring substances sodium glycocholate (bile acid) and lecithin generate a stable colloidal micellar system capable of solubilising the fat-soluble vitamin K1 in an aqueous medium.

The active ingredient, phytomenadione (vitamin K1) has been marketed in Australia since the 1950s as a cremophor formulation for IM injection, Konakion® 1 mg/ 0.5 mL, also containing propylene glycol, phenol and polyethylated castor oil. These latter components have been associated with anaphylaxis following IV use and local irritation when given IM. In 1992 Golding reported an association between intramuscular (but not oral) use of the cremophor formulation and childhood cancer. Subsequent studies of better methodological quality have not confirmed this[13], although a consistent small but non-significant trend towards an increased incidence of acute lymphoblastic leukaemia remained[15] (reviewed by Von Kries 1998, Wariyar et al 2000). Although not licensed for oral use, the cremophor formulation has been used when parents do not wish their infant to receive an intramuscular injection. Gastrointestinal irritation has been a problem with oral use. The production of the cremophor formulation has ceased.

In 2000, the National Health and Medical Research Council (NHMRC)[2] developed the Joint statement and recommendations on Vitamin K administration to newborn infants to prevent vitamin K deficiency bleeding in infancy, in collaboration with the Royal Austr a problem TD nsig si

K prophylaxis to newborns, as well as on the new Konakion® MM Paediatric formulation, and as such the recommendations in the Joint Statement remain current.

This revised Joint Statement has been widely consulted, including receiving

Diagnosis

VKDB includes spontaneous or excessive induced bleeding (eg venipuncture or surgery) at any site associated with decreased activity of the vitamin K dependent coagulation factors (II, VII, IX and X) with normal activity of vitamin K independent factors fibrinogen levels and platelet count (Sutor et al 1999). Confirmation of the diagnosis requires that the coagulation disorder is rapidly reversed following vitamin K administration and that other causes of coagulopathy are excluded.

Classification

VKDB is classified into early, classical and late, based on the age of presentation (Sutor et al 1999, Von Kries 1999).

- **Early VKDB**, occurring on the first day of life, is rare and confined to infants born to mothers who have received medications that interfere with vitamin K metabolism. These include the anticonvulsants phenytoin, barbiturates or carbamazepine, the antitubercular drug rifampicin, and the

Prophylaxis

Konakion® MM is well absorbed orally. With three single doses (administered at days one, seven and 30) blood levels of vitamin K1 are adequate in 89 per cent at 56 days (Greer et al 1998). Proteins that accumulate in the blood when there is a deficiency of vitamin K (PIVKAs) were not detected in the 79 infants who received oral prophylaxis with Konakion® MM.

The only data on effectiveness of oral Konakion® MM comes from Switzerland where since 1995, 93 per cent of infants have received it by this route. The intended regimen was two oral doses of 2 mg, the first on day one and the second on day four. Three years of surveillance data reported by Schubiger et al 1999 found one case of classical VKDB and 11 definite cases of late VKDB in 247,000 cases. Nine of these 11 were found to have underlying liver disease. Of the remaining two, one had no prophylaxis and the other had the recommended two oral doses.

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Appendix: History of the development of the Joint Statement

In 2000, the National Health and Medical Research Council (NHMRC) was requested to: