



COMMON TECHNICAL DOCUMENT

PRODUCT: KETRODOL (PHYTOMENADIONE INJECTION BP)

1.4	Product information
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1.4.1	Prescribing Information (Summary of Product characteristics)- Attached
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1. NAME OF THE MEDICINAL PRODUCT
KETRODOL (PHYTOMENADIONE INJECTION BP)

1.1 PRODUCT NAME:
KETRODOL

1.2 STRENGTH
10 mg/ml

1.3 PHARMACEUTICAL DOSAGE FORM
Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 QUALITATIVE DECLARATION
Phytomenadione Injection BP 10 mg

2.2 QUANTITATIVE DECLARATION
Composition:
Each ml contains:
Phytomenadione BP.....10 mg

3. PHARMACEUTICAL FORM
Solution for Injection

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Treatment of hypertensive emergencies, particularly those associated with pre-eclampsia and toxemia of pregnancy. Treatment of hypertension with renal complications



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4.2 POSOLOGY AND METHOD OF ADMINISTRATION:**Adults**

Severe or life-threatening haemorrhage, e.g. during anticoagulant therapy: The coumarin anticoagulant should be withdrawn and an intravenous injection of Phytomenadione injection BP given slowly (over at least 30 seconds) at a dose of 5 - 10 mg together with prothrombin complex concentrate (PCC). Fresh frozen plasma (FFP) may be used if PCC is not available. The patient's INR should be estimated three hours later and, if the response has been inadequate, the dose should be repeated. Not more than 40 mg of Phytomenadione injection

BP should be given intravenously in 24 hours. Coagulation profiles must be monitored on a daily basis until these have returned to acceptable levels; in severe cases more frequent monitoring is necessary.

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

Anticoagulant	Condition	Intravenous vitamin K ₁	Concomitant therapy
Warfarin	Major bleeding	5.0 mg	PCC ₁
Life threatening bleeding	5.0 to 10.0 mg	PCC ₁	

PCC, prothrombin complex concentrate

₁ Fresh frozen plasma (FFP) may be used if PCC is not available.

Less severe haemorrhage:

Treatment of asymptomatic patients with elevated INR values depends on factors such as the underlying indication for anticoagulation, INR value, length of time spent outside the therapeutic INR range, patient characteristics (e.g. age, comorbidity, concomitant medication), and the associated risk of major bleeding. The following dose recommendations are provided for therapeutic guidance only:

Dose recommendations for vitamin K₁ therapy in patients with asymptomatic high

International Normalized ratio (INR) with or without mild haemorrhage:

Anticoagulant	INR	Intravenous vitamin K ₁
Warfarin	5-9	0.5 to 1.0 mg
>9	1.0 mg	

For small doses one or more ampoules of Phytomenadione Injection Paediatric (2 mg/0.2 ml: same solution) can be used.

Reversal of anticoagulation prior to surgery

Patients who require emergency surgery that can be delayed for 6-12 hours can be given 5 mg intravenous vitamin K₁ to reverse the anticoagulant effect. If surgery cannot be delayed, PCC can be given in addition to intravenous vitamin K₁ and the INR checked before surgery.

Use with anticoagulants other than warfarin

The dosing recommendations above apply to patients taking warfarin. There are limited data



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regarding reversal of the effects of other anticoagulants, such as acenocoumarol or phenprocoumon. The half lives of these anticoagulants are different to warfarin and different doses of vitamin K₁ may be required.

Special dosage instructions***Elderly***

Elderly patients tend to be more sensitive to reversal of anticoagulation with Phytomenadione Injection. The dosage for this patient group should therefore be at the lower end of the ranges recommended.

Instructions for infusion in adults

Phytomenadione Injection Ampoules are for intravenous injection and should be diluted with 55 ml of 5% glucose before slowly infusing the product. The solution should be freshly prepared and protected from light. Phytomenadione Injection Ampoule solution should not be diluted or mixed with other injectables, but may be injected into the lower part of an infusion apparatus.

Children aged 1 to 18 years

It is advisable that a haematologist is consulted about appropriate investigation and treatment in any child in whom Phytomenadione Injection is being considered.

Likely indications for using vitamin K in children are limited and may include:

1. Children with disorders that interfere with absorption of vitamin K (chronic diarrhoea, cystic fibrosis, biliary atresia, hepatitis, coeliac disease).
2. Children with poor nutrition who are receiving broad spectrum antibiotics.
3. Liver disease.
4. Patients receiving anticoagulant therapy with warfarin in whom the INR is increased outside the therapeutic range and therefore are at risk of, or are bleeding, and those with an INR in the therapeutic range who are bleeding.

For patients on warfarin therapy, therapeutic intervention must take into consideration the reason for the child being on warfarin and whether or not anticoagulant therapy has to be continued (e.g. in a child with mechanical heart valve or repeated thromboembolic complications) as vitamin K administration is likely to interfere with anticoagulation with warfarin for 2 – 3 weeks.

It should be noted that the earliest effect seen with vitamin K treatment is at 4 – 6 hours and therefore in patients with severe haemorrhage replacement with coagulation factors may be indicated (discuss with haematologist).

Dose of vitamin K

There are few data available regarding use of Phytomenadione Injection in children over 1 year. There have been no dose ranging studies in children with haemorrhage. The optimal dose should therefore be decided by the treating physician according to the indication, clinical situation and weight of the patient. Suggested dosages based on clinical experience are as follows:

Children with major and life threatening bleeding

A dose of 5 mg vitamin K₁ i.v. is suggested (together with PCC if appropriate, or FFP if PCC

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is not available).

Children with asymptomatic high International Normalised Ratio (INR) with or without mild haemorrhage

Intravenous vitamin K₁ at doses of 30 micrograms/kg have been reported to be effective in reversing asymptomatic high (>8) INR in clinically well children.

The patient's INR should be measured 2 to 6 hours later and if the response has not been adequate, the dose may be repeated. Frequent monitoring of vitamin K dependent clotting factors is essential in these patients.

Neonates and babies

Phytomenadione Injection Paediatric 2 mg/0.2 ml should be used in these patients

4.3 CONTRAINDICATIONS

Use in patients with a known hypersensitivity to any of the constituents.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When treating patients with severely impaired liver function, it should be borne in mind that one Phytomenadione Injection Ampoule 10 mg/1ml contains 54.6mg glycocholic acid and this may have a bilirubin displacing effect. Careful monitoring of the INR is necessary after administration of Phytomenadione Injection in patients with severely impaired liver function.

At the time of use, the ampoule contents should be clear. Following incorrect storage, the contents may become turbid or present a phase separation. In this case the ampoule must no longer be used.

In potentially fatal and severe haemorrhage due to overdosage of coumarin anticoagulants, intravenous injections of Phytomenadione Injection must be administered slowly and not more than 40 mg should be given during a period of 24 hours. Phytomenadione Injection therapy should be accompanied by a more immediate effective treatment such as transfusion of whole blood or blood clotting factors. When patients with prosthetic heart valves are given transfusions for the treatment of severe or potentially fatal haemorrhage, fresh frozen plasma should be used. The use of vitamin K₁ in patients with mechanical heart valves is generally to be avoided, unless there is major bleeding.

Large doses of Phytomenadione Injection (not more than 40 mg per day) should be avoided if it is intended to continue with anticoagulant therapy because there is no experience with doses above this maximum of 40 mg per day and higher doses may give rise to unexpected adverse events. Clinical studies have shown a sufficient decrease in the INR with the recommended dosage. If haemorrhage is severe, a transfusion of fresh whole blood may be necessary whilst awaiting the effect of the vitamin K₁.

Vitamin K₁ is not an antidote to heparin.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No significant interactions are known other than antagonism of coumarin anticoagulants.

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There is no specific evidence regarding the safety of Phytomenadione Injection in pregnancy but, as with most drugs, the administration during pregnancy should only occur if the benefits outweigh the risks. Phytomenadione Injection is not recommended for pregnant women as prophylaxis of vitamin K deficiency bleeding in the newborn.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not Reported.

4.8 UNDESIRABLE EFFECTS

There have been reports of anaphylactoid reactions after intravenous injections of Phytomenadione Injection. Very rarely, venous irritation or phlebitis has been reported in association with intravenous administration. Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 OVERDOSE:

Hypervitaminosis of vitamin K₁ is unknown.
Reintroduction of anti-coagulation may be affected.

5. PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMICS PROPERTIES****Pharmacotherapeutic group****5.1 Pharmacodynamic properties**

Phytomenadione Injection is a synthetic preparation of vitamin K. The presence of vitamin K (i.e. vitamin K or substances with vitamin K activity) is essential for the formation within the body of prothrombin, factor VII, factor IX and factor X. Lack of vitamin K leads to an increased tendency

to haemorrhage. When an antidote to an anticoagulant is necessary it is essential to use vitamin K₁ itself, as vitamin K analogues are much less effective.

Vitamin K₁ is solubilised by means of a physiological colloidal system, also found in the human body, consisting of lecithin and bile acid. Owing to the absence of organic solvents, the Phytomenadione Injection is well tolerated on intravenous administration.

5.2 Pharmacokinetic properties

In blood plasma, 90% of vitamin K₁ is bound to lipoproteins. Following an intramuscular dose of 10mg vitamin K, plasma concentrations of 10 – 20 mcg/l are produced (normal range 0.4 – 1.2 mcg/l). Systemic availability following intramuscular administration is about 50% and elimination



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half-life in plasma is approximately 1.5 – 3 hours.

6. MARKETING AUTHORISATION HOLDER:

RENE PHARMACY (R) LTD

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NYARUGENGE DISTRICT, opp, T-2000 NEW,

B.P.6033, KIGALI, RWANDA.

7. DATE OF FIRST AUTHORISATION RENEWAL OF THE AUTHORISATION:

Not Applicable

8. DATE OF REVISION / APPROVAL OF THE TEXT:

Not Applicable