HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 February 2009

KANOKAD 25 IU/ml of factor IX, powder and solvent for solution for injection
250 IU of factor IX in a vial (type I glass) with a (bromobutyl) stopper + 10 ml of solvent in a vial (type I or type II glass) with a (bromobutyl) stopper and a transfer system, box of 1 (CIP: 573 863-8)
500 IU of factor IX in a vial (type II glass) with a (bromobutyl) stopper + 20 ml of solvent in a vial (type I or type II glass) with a (bromobutyl) stopper and a transfer system, box of 1 (CIP: 573 864-4)

Applicant: LFB-BIOMEDICAMENTS

Human prothrombin complex (PCC)

ATC Code: B02BD01

List I

Medicine for hospital prescription only (on the French “retrocession” [dispensing of drugs to outpatients by hospital pharmacies] list)

Date of Marketing Authorisation via the national procedure: 18 November 2008.

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Human prothrombin complex (PCC)

KANOKAD (concentrate of 4 coagulation factors) nominally contains the following quantities (IU) of the human coagulation factors tabled below:

Ingredient	KANOKAD 250 IU (factor IX)	KANOKAD 500 IU (factor IX)	After reconstitution (IU/ml)
Coagulation factor II	140-350	280-700	14-35
Coagulation factor VII	70-200	140-400	7-20
Coagulation factor IX	250	500	25
Coagulation factor X	140-350	280-700	14-35

The total protein content per vial is 130-350 mg (KANOKAD 250 IU) or 260-700 mg (KANOKAD 500 IU). The specific activity of the product is $\geq$ 0.6 IU/mg expressed in terms of factor IX activity. This medicinal product contains 125-195 mmol/l of sodium per dose.

1.2. Novel aspects

KANOKAD does not contain heparin and is subjected to 15 nm nanofiltration.

1.3. Indication

- "Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, **when rapid correction of the deficiency is required**."

- "Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors, **when purified specific coagulation factor product is not available**".

1.4. Dosage

"The dosage and duration of the substitution therapy depend on the severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition. The individual dosage can be determined only on the basis of regular determinations of the plasma levels of the coagulation factors of interest, or on the basis of global tests of the prothrombin complex levels (prothrombin time, INR) and continuous monitoring of the patient's clinical condition.

- Treatment of bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment: The dose will depend on the INR before treatment, the targeted INR and the body weight. Reference should be made to the published national professional recommendations for the management of vitamin K antagonist overdose.
- Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors, when purified specific coagulation factor product is not available: Calculation of the required dose is based on the empirical notions that approximately 1 IU factor VII or factor IX per kg body weight raises plasma factor VII or IX activity by 0.01 IU/ml, 1 IU factor II per kg body weight raises plasma factor II activity by 0.02 IU/ml and 1 IU factor X per kg body weight raises plasma factor X activity by 0.017 IU/ml.

Recommended dosages are given only as a guide: Cf. SPC section 4.2 Posology and method of administration.

As with all prothrombin complexes, INR levels must be measured[1] before this medicinal product is prescribed or administered."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

B	Blood and blood forming organs
B02	Antihemorrhagics
B02B	Vitamin K and other haemostatics
B02BD	Blood coagulation factors
B02BD01	Coagulation factor IX, II, VII and X in combination

2.2. Medicines in the same therapeutic category

Other human prothrombin complex products:

- KASKADIL, powder and solvent for solution for injection

Indication (Marketing Authorisation):

- "Treatment and prevention of bleeding episodes in cases of global and severe deficiency in vitamin K-dependent factors, as in cases of vitamin K antagonist overdose, when rapid correction of the deficiency is required. For isolated factor VII and IX deficiency, use should be made of specific factor VII or IX concentrates.
- Treatment and prevention of bleeding episodes in cases of congenital factor II or factor X deficiency."

Contraindication: "Known allergy to any of the ingredients of the product, particularly recent history of heparin-induced immuno-allergic thrombocytopenia."

- OCTAPLEX[2], powder and solvent for solution for injection

Indication (Marketing Authorisation):

- "Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.
- Treatment of bleeding and perioperative prophylaxis in constitutional deficiency of the vitamin K dependent coagulation factors II and X when purified specific coagulation factor product is not available."

Contraindications: - Hypersensitivity to the active substance or to any of the excipients - Known allergy to heparin or history of heparin-induced thrombocytopenia

2.3. Medicines with a similar therapeutic aim

In congenital coagulation factor VII deficiency:
- Activated eptacog alfa (NOVOSEVEN)

Note. Human factor VII (FACTEUR VII LFB) has not been available on the market since 15 January 2009.

In congenital coagulation factor IX deficiency (haemophilia B):
- Plasma-derived factor IX: BETAFACT; MONONINE; OCTAFIX
- nonacog alfa (BENEFIX)

In acquired deficiencies in vitamin K-dependent coagulation factors (vitamin K antagonist overdose):
- Fresh frozen plasma has the status of an unstable blood product (= non medicine); it is administered as a last resort in these situations

[1] INR measurement is included in the Nomenclature des Actes de Biologie Médicale [Nomenclature of Procedures in Laboratory Medicine] (NABM 0127)

[2] Two steps to ensure biological safety (solvent/detergent treatment and nanofiltration) are carried out during the manufacture of OCTAPLEX (50 nm nanofiltration) and KANOKAD (15 nm nanofiltration), and a single step (solvent/detergent treatment) for KASKADIL

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical data submitted by the pharmaceutical company are those contained in the Marketing Authorisation registration dossier for the medicinal product COFACT. Indeed, KANOKAD is similar to the medicinal product COFACT which has been marketed by SANQUIN in the Netherlands for several years.

In view of the significant lookback period in respect of the efficacy and tolerance of PCCs and the comparability of COFACT with the previous PCC[3] (PCC-SD) manufactured by SANQUIN (apart from the additional nanofiltration carried out during the manufacture of COFACT), only one clinical study was conducted specifically with COFACT for the registration dossier: this was the KB 98005[4] study, the objective of which was to compare the efficacy and tolerance of two COFACT dosage regimens in patients treated with vitamin K antagonists. This study also included a pharmacokinetics phase (addendum to study n° KB 98005).

The indication of COFACT in "congenital deficiency of one of the vitamin K-dependent coagulation factors, when a specific coagulation factor concentrate is not available" has not been the subject of a clinical study because, according to the pharmaceutical company, of the low prevalence of factor II and X deficiency and the availability of specific factor VII and factor IX.

In summary, no clinical data are available permitting a comparison of the efficacy of KANOKAD with that of other PCCs. It is not therefore possible to rate any additional therapeutic benefit it may have, notably by comparison with OCTAPLEX.

3.2. Adverse effects

COFACT has been available on the market (notably in the Netherlands) since 1 October 1997. Two periodic safety update reports are available, covering the periods:

- from 1 October 1997 to 1 October 2002
- from 1 October 2002 to 1 August 2006

No changes were made to the adverse effects section of the Summary of Product Characteristics (SPC) during these periods.

3.3. Conclusion

KANOKAD is identical to COFACT, a prothrombin complex product which has been available on the market in the Netherlands since 1997. No clinical data are available enabling the therapeutic benefit of KANOKAD to be evaluated by comparison with the other prothrombin complex products available in France (OCTAPLEX and KASKADIL).

[3] the results of three studies conducted with the preceding-generation PPSB (PCC-SD) are not commented on insofar as they do not enable the significance of the effect of KANOKAD to be evaluated by comparison with other prothrombin complex medicinal products: two tolerance and pharmacokinetic studies (Study no. 035-003 and Study no. 035-007) and one study comparing the efficacy of two dosage regimens (Study no. KB 94002)

[4] Van Aart L, Eijkhout HW, Kamphuis JS, Dam M et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: An open, prospective randomized controlled trial. Thrombosis Research (2006) 118, 313-320

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Congenital deficiencies of vitamin K-dependent coagulation factors are generally serious diseases which can be life-threatening. All deficiencies in one of the vitamin K-dependent coagulation factors can have clinical manifestations, particularly in their severe forms. Combined coagulation factor deficiencies caused by a disorder of vitamin K metabolism are very rare.

Acquired deficiencies in several prothrombin complex factors can occur during treatment with vitamin K antagonists or in case of vitamin K deficiency. When the deficiency becomes severe, retroperitoneal and cerebral bleeding may be observed.
Severe liver failure can also cause a perceptible reduction in prothrombin complex levels and a marked bleeding tendency, with a clinical picture which may involve intravascular coagulation.
These different situations can be life-threatening.

KANOKAD is a first-line agent intended as curative therapy (treatment) and for the preventive treatment (perioperative prophylaxis) of bleeding episodes:

- in acquired deficiency of the prothrombin complex coagulation factors when rapid correction of the deficiency is required
- in congenital deficiency of one of the vitamin K-dependent coagulation factors when a specific high purity coagulation factor is not available

Public health benefit

The clinical situations concerned can be life-threatening. They represent a moderate public health burden.
In view of the current prognosis for these clinical situations associated with standard management, a therapeutic need exists in terms of public health.
However, in view of the data from the clinical trials and taking into account the existing treatments, there is no evidence to suggest that KANOKAD can be expected to have an additional impact in terms of morbidity/mortality and quality of life.
Consequently, it is not expected that KANOKAD will benefit public health.

The efficacy/adverse effects ratio for this medicinal product is high.
Alternative pharmacological treatments exist.

Conclusion: The actual benefit of KANOKAD 250 IU/10 ml and 500 IU/20 ml in their two indications is substantial.

4.2. Improvement in actual benefit (IAB)

KANOKAD 250 IU/10 ml and 500 IU/20 ml do not provide any improvement in actual benefit (IAB level V).

The Committee nevertheless notes the benefit of having KANOKAD available, because of its heparin-free formulation, as it represents a useful alternative for the management of patients with a history of heparin-induced thrombocytopenia.

4.3. Therapeutic use

4.3.1 Acquired prothrombin complex coagulation factor deficiency

Acquired deficiencies in the vitamin K dependent coagulation factors are often the result of a vitamin K antagonist overdose.

Correcting a deficiency in vitamin K dependent coagulation factors is based on the administration of vitamin K (via the oral or parenteral route). This corrective treatment takes several hours, however, depending on the extent of hypercoagulability and the functional capacity of the liver. This delay is incompatible with the patient's management when rapid correction is required (active bleeding or invasive / surgical procedure which cannot be postponed). In these situations, the only way to restore haemostasis within a matter of minutes is to administer the deficient factors directly via the intravenous route. This is the first-line treatment, which must always be accompanied by concomitant administration of vitamin K. Haemorrhagic shock, where it exists, must be treated in parallel. KANOKAD (like the other human prothrombin complex products) is therefore indicated when urgent correction of the deficiency is required.

Procedure to be followed in cases of serious bleeding according to the HAS recommendations[5]

- Serious, or potentially serious, bleeding within the context of treatment with vitamin K antagonists is defined by the presence of at least one of the following criteria:
  - External bleeding which cannot be controlled by the usual means
  - Haemodynamic instability: Systolic arterial BP > 90 mmHg or reduction of 40 mmHg in relation to the systolic arterial BP, or mean arterial pressure < 65 mmHg, or any sign of shock
  - Need for rapid haemostatic treatment: Surgery, interventional radiology, endoscopy
  - Need for transfusion of red cell concentrates
  - Life- or function-threatening site, e.g.:
    - Intracranial and intraspinal bleeding
    - Intra-ocular and retro-orbital bleeding
    - Haemothorax, haemo- and retroperitoneum, haemopericardium
    - Haematoma of the deep muscles and/or compartment syndrome
    - Acute gastrointestinal bleeding
    - Haemarthrosis

If none of these criteria exist, the bleeding is classified as non-serious.

- Medicines which can be used: Vitamin K and prothrombin complex concentrates (KANOKAD, KASKADIL and OCTAPLEX) are the most appropriate pharmacological treatments. Unless a PCC is not available, fresh frozen plasma should not be used for the sole purpose of counteracting the effects of vitamin K antagonists (grade B). Activated recombinant factor VII (eptacog alpha: NovoSeven) should not be used for the purpose of counteracting the effects of vitamin K antagonists (grade C).

- Serious bleeding requires hospital treatment. The existence of multidisciplinary organisational procedures improves the speed and quality of management (evidence level 3). Such procedures should be formalised. The need for a surgical, endoscopic or endovascular haemostatic procedure must be discussed rapidly with the surgeons and radiologists.

[5] Argumentaires des recommandations professionnelles: prise en charge des surdosages en antivitamines K, des situations à risque hémorragique et des accidents hémorragiques chez les patients traités par antivitamines K en ville et en milieu hospitalier. **POURQUOI PAS DE TRADUCTION DE CE TITRE** HAS (service des bonnes pratiques professionnelles), Avril 2008. Published in: STV 2008; 20, special edition, July 2008

In cases of serious bleeding, normal haemostasis (targeted INR of 1.5 or less) must be restored within the shortest possible time (a few minutes).
The following is recommended:

- Discontinuation of the vitamin K antagonist
- Rapid administration of PCC and vitamin K (grade C)
- Standard treatment for possible massive haemorrhage at the same time (correction of hypovolaemia, transfusion of red cell concentrates if necessary, etc.)

In the absence of a rapid supply system, a reserve of a few vials of PCC should be kept in the hospital departments concerned, notably in accident and emergency departments, intensive care units and certain operating theatres, in agreement with the pharmacy and in compliance with traceability requirements.

In the event of unscheduled emergency surgery or invasive procedures with a risk of bleeding, the HAS recommendations are as follows:

- Measure the INR on admission of the patient and administer 5 mg vitamin K
- If the time required for the intervention is not sufficient for adequate haemostatic function to be achieved (target INR < 1.5 and 1.2 for neurosurgery) with vitamin K alone, administer PCC and check the INR before the intervention
- Check the INR between 6 and 8 hours after the intervention with the same post-operative management as for elective interventions

Note. Emergency surgery is defined as a procedure which has to be performed within a time which is not sufficient for adequate haemostatic function to be achieved (target INR < 1.5 and 1.2 for neurosurgery) with vitamin K administration alone.

4.3.2 Congenital deficiencies in the prothrombin complex coagulation factors

According to the data from the ORPHANET database:

- Constitutional factor II or prothrombin deficiency[6] "is exceptional. It is the rarest coagulation factor deficiency. It is transmitted as an autosomal recessive trait. Heterozygous subjects are asymptomatic. Homozygous and double heterozygous subjects have moderate bleeding problems in the form of bruising, epistaxis and postoperative or post-traumatic bleeding
Treatment of bleeding with plasma concentrates which are rich in factor II is rarely necessary".

- Factor VII (FVII) deficiency[7] is "a rare inherited bleeding disorder caused by decreased levels of or absence of coagulation factor VII. It has a prevalence of 1/400,000. The clinical manifestations are very variable and the severity of the bleeding disorder does not correlate with residual FVII activity levels. The clinical manifestations may be very severe with the early occurrence of intracerebral haemorrhages, or haemarthrosis, or else moderate with mucocutaneous bleeding (epistaxis, menorrhagia) or bleeding provoked by surgery. Finally, many subjects are completely asymptomatic despite having very low FVII levels. This disorder is transmitted as an autosomal recessive trait. Only homozygous or doubly heterozygous patients can have bleeding problems, with heterozygous subjects being asymptomatic. Analysis of the FVII gene has enabled more than 130 different mutations to be described: these are mainly point mutations, usually within a single family.
At present, treatment is by replacement, with administration of FVII concentrate, although pre-operative patient selection remains difficult in subjects with few or no symptoms"

- The management of haemophilia B (congenital factor IX deficiency) makes use of high purity plasma-derived factor IX products or recombinant factor IX.

[6] Dr I. Martin (August 2002), Orphanet
[7] Dr M. Giansily-Blaizot (June 2004), Orphanet.

- Constitutional coagulation factor X, or Stuart-Prower factor, deficiency[8] "is a very heterogeneous bleeding disorder, both clinically and genetically. Factor X deficiency is transmitted as an autosomal recessive trait. Severe deficiencies are exceptional. The genetic abnormalities involved are varied. Heterozygotes are generally asymptomatic. In people with severe deficiencies, haemarthrosis (bleeding into joints) and cerebro-meningeal bleeding are described.
The treatment of severe bleeding or prophylaxis for the risk of perioperative bleeding is based on transfusions of red cell concentrates rich in factor X".

In practice, human prothrombin complexes are used mainly in cases of severe congenital factor II (prothrombin) and X deficiencies. The treatment strategy is established in consultation with a specialist in haemostasis or a doctor from the Regional Haemophilia Treatment Centre (Centre Régional de Traitement de l'Hémophilie).

In patients with a congenital deficiency of one of the vitamin K-dependent factors, KANOKAD (OCTAPLEX or KASKADIL) use should be exceptional: It is reserved for the rare situations in which a specific coagulation factor concentrate cannot be made available rapidly for the treatment of severe bleeding or perioperative (urgent) prophylaxis for severe bleeding. It should be noted that no study has evaluated the efficacy of PCCs (including KANOKAD) in patients with congenital factor II or X deficiency.

- Furthermore, because the KANOKAD formulation does not contain heparin, KANOKAD represents a useful alternative to OCTAPLEX (and to KASKADIL) in patients with a history of heparin-induced thrombocytopenia or in cases of known allergy to heparin and requiring the prescription of a human prothrombin complex, OCTAPLEX and KASKADIL being contra-indicated.

4.4. Target population

4.4.1 Acquired deficiencies in vitamin K-dependent coagulation factors

The target population for KANOKAD in this indication corresponds mainly to situations associated with bleeding or risk of bleeding under vitamin K antagonists, when rapid correction of the deficiency is required.

Quantitative estimate:
The number of patients treated with vitamin K antagonists in France has been estimated at about 1% of the French population (600,000 patients according to the 2008 HAS recommendations, ref. 8).
- Approximately 17,000 hospital admissions each year are attributable to the haemorrhagic complications of this type of treatment (Afssaps data, Internet site, 2008)
- Prospective studies of European cohorts indicate an annual incidence of serious haemorrhagic complications of between 1.1% in young subjects and 2.1% in elderly subjects in Italy and 2.7% in the Netherlands (data submitted by the pharmaceutical company)
- The frequency of serious haemorrhagic events has been estimated at between 1.2% and 5.6 % per patient/year, or between 7,200 and 33,600 patients/year likely to be treated with OCTAPLEX or KASKADIL in 2005 (Ref. Committee Opinion dated 22 June 2005, OCTAPLEX). This estimate may be considered as still being valid in 2008 for KANOKAD

4.4.2 Congenital deficiency in vitamin K-dependent coagulation factors when a specific coagulation factor is not available

In view of the fact that specific factor VII and IX products are available in France, the target population for KANOKAD in this indication corresponds mainly to patients who are deficient in factor II, factor X or a combination of the four vitamin K-dependent coagulation factors.

[8] Dr I. Martin (August 2002)*, Orphanet

Quantitative estimate:
- Factor II deficiency: the prevalence of this deficiency is estimated at 1 per 2 million[9], or about 37 patients in France.
- Factor X deficiency: the prevalence of this deficiency is in the order of 1/1, 000,000 in the general population[10], or about 64 patients in France. The latest descriptive data published in 2005 by Réseau FranceCoag identified 7 patients with a factor X deficiency in the French cohort[11].
- Deficiency in a combination of all the vitamin K-dependent coagulation factors: this situation is extremely rare[12] (fewer than twenty families in the world affected by this deficiency).

In practice, the number of patients likely to receive KANOKAD in this indication is very small and cannot be precisely estimated in France.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation.

[9] Peyvandi F, Mannucci PM. Rare coagulation Disorders. Thromb Haemost 1999;82:1207-14
[10] Bolton-Maggs PHB, Perry DJ, Chalmers EA, Parapias LA, Wilde JT, Williams MD, Collins PW, Kitchen S, Dolans G, Mumford AD. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. Haemophilia 2004; 10: 593-628
[11] Réseau FranceCoag. Cohorte française des patients atteints de maladies hémorragiques par déficits héréditaires en protéines de la coagulation. Données descriptives 2005. http://www.francecoag.org/pdfs/Donnees_descriptives_2005.pdf
[12] Bolton-Maggs PHB et al. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. Haemophilia 2004; 10: 593-628