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Autoridade Nacional do Medicamento
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Summary Public Assessment Report

Generics

Folinato de cálcio Kabi

10 mg/mL, solution for injection or infusion

(Calcium Folinate)

PT/H/1204/001/DC

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This is a summary of the public assessment report (PAR) for Folinato de cálcio Kabi. It explains how Folinato de cálcio Kabi was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Folinato de cálcio Kabi.

For practical information about using Folinato de cálcio Kabi, patients should read the package leaflet or contact their doctor or pharmacist.

What is Folinato de cálcio Kabi and what is it used for?

Folinato de cálcio Kabi is a 'generic medicine'. This means that Folinato de cálcio Kabi is similar to a 'reference medicine' already authorised in the European Union (EU) called Folinovo, 10 mg/ml, Injectable Solution from Hospira Portugal, Lda.

Calcium Folinate is used to:

- reduce the harmful effects and treat overdose of certain types of anti-cancer medicines for instance methotrexate and other folic acid antagonists. This is known as "calcium folinate rescue".

- treat cancer in combination with 5-fluorouracil (an anti-cancer medicine). 5-fluorouracil works better when it is given together with Calcium Folinate.

How does Folinato de cálcio Kabi work?

Calcium Folinate 10 mg/ml solution for injection or infusion contains calcium folinate, which is one of a group of medicine called detoxifying agents. It is a calcium salt of folinic acid, which is related to the vitamin folic acid.

How is Folinato de cálcio Kabi used?

The pharmaceutical form of Folinato de cálcio Kabi is solution for injection or infusion and the route of administration is intravenous and intramuscular.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

What benefits of Folinato de cálcio Kabi have been shown in studies?

No additional studies were needed as Folinato de cálcio Kabi is a generic medicine that is given by intramuscular injection / intravenous injection or infusion and contains the same active substance as the reference medicine, called Folinovo, 10 mg/ml, Injectable Solution,.

What are the possible side effects of Folinato de cálcio Kabi?

Because Folinato de cálcio Kabi is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

Why is Folinato de cálcio Kabi approved?

It was concluded that, in accordance with EU requirements, Folinato de cálcio Kabi has been shown to have comparable quality and to be bioequivalent/be comparable to Folinovo, 10 mg/ml, Injectable Solution. Therefore, the INFARMED, I.P. decided that, as for reference medicine called Folinovo, 10 mg/ml, Injectable Solution, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Folinato de cálcio Kabi?

A Risk Management Plan - Version 0.0, dated 11-08-2014 - has been developed to ensure that Folinato de cálcio Kabi is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Folinato de cálcio Kabi including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/ reviewed continuously as well.

Other information about Folinato de cálcio Kabi

The marketing authorisation for Folinato de cálcio Kabi was granted on 19-11-2015.

The full PAR for Folinato de cálcio Kabi can be found on the website http://www.infarmed.pt/infomed/inicio.php. For more information about treatment with Folinato de cálcio Kabi, read the package leaflet or contact your doctor or pharmacist.

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Public Assessment Report

Scientific discussion

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This module reflects the scientific discussion for the approval of Folinato de cálcio Kabi. The procedure was finalised at 15-10-2015. For information on changes after this date please refer to the module 'Update'.

I. Introduction

Based on the review of the quality, safety and efficacy data, the Member States have agreed in granting a marketing authorisation for Folinato de cálcio Kabi 10 mg/mL, solution for injection or infusion, from Fresenius Kabi Deutschland GmbH.

The product is indicated for

- to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, this procedure is commonly known as "Calcium Folinate Rescue".

- in combination with 5-fluorouracil in cytotoxic therapy.

A comprehensive description of the indications and posology is given in the SmPC."

The marketing authorization was granted on 19-11-2015 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Fresenius Kabi Deutschland GmbH, Germany.

II. Quality aspects

II.1 Introduction

Folinato de cálcio Kabi 10 mg/mL, solution for injection or infusion:

This medicine is a solution for injection or infusion. It is a clear, yellowish solution, free from visible particles.
The Pharmaceutical form is solution for injection or infusion

The excipients are: Sodium chloride, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment) and water for injections

Folinato de cálcio Kabi 10 mg/mL, solution for injection or infusion is available in amber coloured Ph. Eur Type I glass vial, with chlorobutyl rubber stopper and sealed with red, yellow, violet, white, brown and orange aluminium flip-off seal, containing 5 ml, 10 ml, 20 ml, 35 ml, 50 ml or 100 ml solution for injection or infusion, respectively. However, color of flip-off aluminium seals may change depending on the marketing requirement.

Pack sizes:
The packages contain either 1, 5 or 10 vials of 5 ml, 10 ml, 20 ml, 35 ml, 50 ml or 100 ml, respectively.

Not all pack sizes may be marketed

II.2 Drug Substance

Drug Substance: Calcium folinate Ph. Eur.

Chemical name: Calcium (2S)-2-[[4-[[[(6*RS*)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8 – hexahydropteridin -6-yl]methyl]amino]benzoyl]amino]pentanedioate.

Calcium folinate is a 1:1 mixture of (6R) - and (6S) - isomers, the diastereoisomers of the 5-formyl derivate of tetra-hydrofolic acid. The (6S) - isomer is the biologically active part of the calcium folinate. The glutamic moiety coming from starting material folic acid is L-glutamic.

It is a white to light yellow crystalline powder. It is sparingly soluble in water, practically insoluble in acetone and in ethanol (96%).

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to calcium folinate are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 18 months when stored between 2°C – 8°C in original carton, protected from light for the drug product packed in type I glass vials is considered acceptable.

III. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of calcium folinate are well known. As calcium folinate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

This medicinal product is unlikely to result in significant risk to the environment. Calcium folinate is an active metabolite of folinic acid.
Folic acid is considered a member of the vitamin B complex and it is a natural component.
Considering the guideline on the environmental risk assessment of medicinal products for human use (Doc. Ref. EMEA/CHMP/SWP/4447/00 corr 1*) an ERA is not required for this medicinal product.

IV. Clinical aspects

IV.1 Introduction

To support the application, the Applicant has not conducted any clinical studies with *Calcium Folinate* and all the relevant clinical information provided in the section 2.5 (Clinical overview) is literature based.
The drug product is an aqueous solution for intramuscular or intravenous use; hence, a bioequivalence study was not performed. Based on the description, composition properties of the drug product, and the product development process no other issues can be raised. Therefore, there is no premise to support the hypothesis that this generic calcium folinate solution will exhibit a pharmacological/toxicological profile different from that presented in the clinical summary.

IV.2 Risk Management Plan

The MAH has submitted a risk management plan - Version 0.0, dated 11-08-2014 - in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Folinato de cálcio Kabi 10 mg/mL, solution for injection or infusion.

IV.3 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

V. User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to CALCIUMFOLINAT "ACTAVIS" 10 mg solution for injection/infusion The bridging report submitted by the applicant has been found acceptable.

VI. Overall conclusion, benefit/risk assessment and recommendation

The application for Folinato de cálcio Kabi 10 mg/mL, solution for injection or infusion contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.