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Summary of the risk management plan (RMP) for Fexeric (ferric citrate coordination complex)

This is a summary of the risk management plan (RMP) for Fexeric, which details the measures to be taken in order to ensure that Fexeric is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Fexeric, which can be found on Fexeric's EPAR page.

Overview of disease epidemiology

Fexeric is a medicine used to control hyperphosphataemia (high levels of phosphate in the blood) in adults with long-term kidney disease.

Patients with severe kidney disease cannot eliminate phosphate absorbed from their diet. This leads to hyperphosphataemia (high blood phosphorus levels), which, in the long term, can cause complications such as heart and bone diseases.

Between 4 and 12 persons in 100 in the EU are estimated to have moderate to severe degrees of long-term kidney disease. The likelihood of high blood phosphorus levels increases with worsening kidney function, and around half of patients with the most severe degree of kidney disease have been reported to have blood-phosphorus levels above normal.

In addition, patients with long-term kidney disease typically develop iron deficiency and/or anaemia. This is caused by many factors including the chronic blood loss associated with a dialysis procedure (used to filter waste products from the blood), blood loss from stomach and intestines, low amount of iron in the diet and poor absorption of dietary iron from food. Treatment with Fexeric can also help to improve iron stores.

Summary of treatment benefits

Fexeric was shown to be effective at controlling blood phosphate levels in 2 main studies in patients with long-term kidney disease and hyperphosphataemia. Both studies looked at the change in the amount of phosphate in the blood, measured in mg/dl.

In the first study, Fexeric was as effective as sevelamer carbonate, an approved medicine, in lowering phosphate levels in 359 patients with long-term kidney disease: after 12 weeks both treatments resulted in a reduction in phosphate levels of around 2 mg/dl.

In the second study, 149 patients who were not on dialysis received either Fexeric or placebo for 3 months. The study showed that blood-phosphate levels fell on average by 0.7 mg/dl with Fexeric compared with 0.3 mg/dl with placebo.

Unknowns relating to treatment benefits

Although the experience with Fexeric in patients over the age of 75 years is limited, the efficacy of Fexeric is not expected to be different in this patient population.

Long-term experience with Fexeric in patients on peritoneal dialysis (a type of dialysis via the membrane lining the inside of the belly) as well as in patients not on dialysis is limited. There is no evidence to suggest that results would differ after long and short-term administration.

Fexeric has not been studied in children and adolescents (less than 18 years old).

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Inflammation, bleeding and erosion in the gut (Gastrointestinal inflammation, bleeding and erosion)	Gastrointestinal effects such as gastrointestinal inflammation, bleeding and erosion are attributed to the direct local inflammatory and erosive effect of iron on the lining of the stomach and intestines. The administration of Fexeric may worsen the symptoms of active severe gastrointestinal disorders (e.g. gastrointestinal bleeding).	Fexeric should not be used in people with active severe bleeding from the stomach and intestines.
High aluminium levels in the blood due to interaction with medications containing aluminium (Hyperaluminaemia due to interaction of aluminium-containing drugs and citrates)	Fexeric contains citrate which may promote the absorption of aluminium. The absorption of too much aluminium in the blood can be toxic (affecting the brain, bones and muscles).	Fexeric should not be taken at the same time as aluminium-containing medicines.
Low phosphorus level in the blood (hypophosphataemia)	Fexeric is used to control hyperphosphataemia by preventing absorption of dietary phosphate. Therefore, there is a risk that the level of phosphorus in the blood may become too low. Low phosphorus levels may result in muscle weakness, bone pain, confusion and muscle breakdown.	Checking phosphorus levels periodically should help detect low levels early. Fexeric should not be used in people with low phosphorus levels in the blood.
The effects of ciprofloxacin may be reduced by Fexeric (reduction in the	The levels of ciprofloxacin in the blood are reduced when ciprofloxacin is administered at the same time as Fexeric. However there is no	Ciprofloxacin should not be taken at the same time as Fexeric, but at least 2 hours before or after Fexeric

Risk	What is known	Preventability
therapeutic use of co-administered ciprofloxacin)	interaction when Fexeric and ciprofloxacin were taken 2 hours apart	

Important potential risks

Risk	What is known
Excess iron in the body / liver toxicity (iron accumulation/ hepatotoxicity)	Patients treated with Fexeric may be at increased risk of excess iron in the body. This is because Fexeric contains iron and patients receiving Fexeric may also receive other iron-containing medicines. The body does not have a natural way to remove excess iron, which can damage important organs such as liver and heart. Regular testing may help in detecting iron accumulation early. Other iron-containing medicines may need to be stopped or have their dose reduced if iron starts to build up in the body.
Overdose in children (Potential for harm from overdose in children)	Iron overdose is dangerous, particularly in children, and requires immediate attention. If a child accidentally takes Fexeric, a doctor or poison control centre should be contacted immediately.
Use in an unapproved age group: children (Potential for paediatric off-label use)	There is a possibility that despite not being approved in this age group, Fexeric may be used in children. Fexeric is not recommended in children below the age of 18 years. The marketing authorisation holder for this medicine plans to evaluate the safety of Fexeric in children.
Reduction in the therapeutic effect of medicines given at the same time as Fexeric (Reduction in the therapeutic effect of co-administered doxycycline, cefdinir, valproate, sertraline , alendronate, levodopa, methotrexate and thyroxine)	Fexeric can attach to other medications in the gut and potentially reduce their absorption. Certain medicines given by mouth can be affected by treatment with Fexeric: • ciprofloxacin, doxycycline, cefdinir: medicines to treat bacterial infections • valproic acid: a medicine to treat epilepsy and mental disorders • sertraline: a medicine to treat and prevent depression • methotrexate: a medicine to treat severe joint inflammation, cancer and the skin disease psoriasis • alendronate: a medicine to treat decreased bone mass and density • levodopa: a medicine to treat Parkinson's disease • levothyroxine: a medicine to treat thyroid hormone deficiency. In some cases where Fexeric needs to be taken as well as another medicine given by mouth, the doctor may advise the patient to take the medicine at least two hours before or after Fexeric. The doctor may also check if the effectiveness of the other medicines is affected.

Missing information

Risk	What is known
Limited information on use in pregnant and breast-feeding women	Fexeric has not been evaluated in pregnant women and in women who are breast-feeding. Fexeric is not recommended in pregnant women, nor in women who could become pregnant unless they are using reliable contraceptive methods, because the risk to the foetus is unknown at this time. A decision must be made whether to stop breast-feeding or to stop or avoid Fexeric therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother.
Limited information on the potential influence on fertility	No data are available on the potential influence of Fexeric on fertility.
Limited information on use in children	Fexeric has not been evaluated in children. The marketing authorisation holder plans to evaluate the safety of Fexeric in children.
Limited information on use in elderly (over 75 years old)	The number of patients over 75 years old in the studies was small. In the clinical studies, elderly patients were treated according to the recommended dosing regimen without any safety concerns.
Limited information on long term safety in patients with chronic kidney disease (a) not on dialysis, and (b) on peritoneal dialysis	The study of Fexeric in patients with long-term kidney disease not on dialysis was of short duration. There is no safety signal to indicate that the safety of Fexeric is different in the dialysis and non-dialysis population. The number of subjects on peritoneal dialysis treated with Fexeric in long term studies was small. There is no safety signal to indicate that the safety of Fexeric is different in the haemodialysis (blood filtration by an external filter) and peritoneal dialysis population. A study evaluating long-term treatment with Fexeric is ongoing.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Fexeric can be found on Fexeric's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
KRX-0502-401	To evaluate the long term safety of KRX-0502 when used in normal clinical practice. To confirm safety in long-term administration in post-authorisation for up to 2 years in haemodialysis, peritoneal dialysis and non-dialysis patients with chronic kidney disease and in patients over 75 years old	Incidence of gastrointestinal inflammation, bleeding and erosion Hypophosphataemia Iron accumulation/ liver toxicity Use in elderly (over 75 years old) High aluminium levels in the blood due to interaction with medications containing aluminium and citrate contained in Fexeric Long-term safety in patients with chronic kidney disease (a) not on dialysis, and (b) on peritoneal dialysis	Planned	Final report to be submitted by 31 December 2020.
RIO-PMS-JT-001	To confirm safety (in particular regarding iron accumulation) in long-term administration in post-marketing for one year or more in haemodialysis, peritoneal dialysis and non-dialysis patients with chronic kidney disease	Incidence of gastrointestinal inflammation, bleeding and erosion Hypophosphataemia Iron accumulation/ liver toxicity Use in elderly (over 75 years old) Long term safety in patients with chronic kidney disease (a) not on dialysis, and (b) on peritoneal dialysis	Planned	Final report: Q4 2021
Study KRX-0502-306	To evaluate the long-term safety of Fexeric in patients not on dialysis	Incidence of gastrointestinal inflammation, bleeding and erosion Hypophosphataemia Iron accumulation/ liver toxicity Use in elderly (over 75 years old)	Started	Final report:Q4 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		Long-term safety in patients with chronic kidney disease (a) not on dialysis, and (b) on peritoneal dialysis		
KRX-0502-JTOX-003 (non-clinical)	To assess the toxicity of orally administered ferric citrate in juvenile rats	Safety in children	Planned start: June 2015	Final report: March 2016
KRX-0502-101	To evaluate safety and tolerability of ferric citrate in children from 6 months to less than 18 years of age	Safety in children	Planned start: September 2015	Final report: September 2019

Studies which are a condition of the marketing authorisation

Study KRX-0502-401 is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 08-2015.