ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Fexeric 1 g film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 g of ferric citrate coordination complex (equivalent to 210 mg of ferric iron).

Excipients with known effect:
Each film-coated tablet contains sunset yellow FCF (E110) (0.99 mg) and Allura Red AC (E129) (0.70 mg).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Peach-coloured, oval shaped, film-coated tablet, embossed with "KX52". Tablets are 19 mm long, 7.2 mm thick and 10 mm wide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fexeric is indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD).

4.2 Posology and method of administration

Posology

Starting dose

The recommended starting dose of Fexeric is 3 to 6 g (3 to 6 tablets) per day based on serum phosphorus levels.

CKD patients who are not on dialysis require the lower starting dose, 3 g (3 tablets) per day.

Fexeric must be taken in divided doses with or immediately after meals of the day.

Patients previously on other phosphate binders who are switched to Fexeric should start taking 3 to 6 g (3 to 6 tablets) per day.

Patients receiving this medicine should adhere to their prescribed low phosphate diets.

Dose titration

Serum phosphorus concentrations should be monitored within 2 to 4 weeks of starting or changing the dose of Fexeric, and approximately every 2-3 months when stable. The dose can be increased or

decreased by 1 to 2 g (1 to 2 tablets) per day at 2- to 4-week intervals as needed to maintain serum phosphorus at recommended target levels up to a maximum of 12 g (12 tablets) per day.

There are limited data available for doses higher than 9 g (9 tablets) per day in CKD patients not on dialysis; therefore in this population doses higher than 9 g/day should be used with caution.

Temporarily discontinue Fexeric if the serum phosphorus is < 3 mg/dl and resume at a lower dose once the serum phosphorus has returned to the target range.

Treatment with Fexeric may lead to elevations in iron stores, particularly in patients receiving concomitant intravenous iron therapy. Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/ml (see section 4.4).

Long term safety data are limited in non-dialysis and peritoneal dialysis (PD) patients (see section 5.1).

Paediatric population

The safety and efficacy of Fexeric in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Elderly population

Fexeric has been administered to over 400 patients ≥ 65 years of age in studies where the dose was titrated to achieve target serum phosphorus levels. The elderly patients were treated according to the recommended dosing regimen without any safety concerns. Experience from clinical studies in patients above the age of 75 years is limited.

Hepatic impairment

Experience from clinical studies in patients with hepatic impairment is limited. No dosage reduction is considered necessary but patients with hepatic impairment should initiate treatment with the lower starting dose, 3 g (3 tablets) per day (see section 5.1).

Method of administration

For oral use. Tablets should be taken whole.
Patients must take Fexeric with or immediately after meals. The total daily dose should be divided across the meals of the day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypophosphataemia
- Active severe gastrointestinal disorders (e.g. gastrointestinal bleeding)
- Haemochromatosis or laboratory tests indicating possible haemochromatosis
- Other iron overload (primary or secondary) syndromes

4.4 Special warnings and precautions for use

Monitoring iron parameters

Increases in ferritin and transferrin saturation (TSAT) are observed with Fexeric use. This medicine should be used only in the absence of iron overload syndromes and with caution if serum ferritin rises above 500 ng/ml. Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/ml. Significantly elevated ferritin levels were observed particularly when concomitant intravenous iron was used.

All patients receiving this medicine require at least quarterly monitoring of serum iron storage parameters (serum ferritin and TSAT). Serum ferritin and TSAT levels increase after intravenous iron administration; hence, blood samples for measurement of iron storage parameters should be obtained at a time appropriate to reflect the patient's iron status after intravenous iron dosing taking into account the product used, the amount of iron given and the frequency of dosing, but a minimum of 7 days after intravenous iron dosing.

Patients treated with Fexeric should not receive concomitant treatment with other oral iron preparations.

Reductions in intravenous iron and erythropoiesis-stimulating agent (ESA) use with this medicine have been observed. Therefore, patients may need reduction in, or discontinuation of, intravenous iron and/or ESAs.

Inflammatory bowel disease

Patients with active, symptomatic inflammatory bowel disease were excluded from clinical trials. Fexeric should only be used in these patients following careful assessment of benefit/risk.

General

Each 1 g film-coated tablet contains sunset yellow FCF (E110) (0.99 mg) and Allura Red AC (E129) (0.70 mg) which may cause allergic reaction.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Fexeric

Results from subgroup analyses in the pivotal clinical study in dialysis patients show that the concomitant use of frequently co-prescribed medications in CKD patients (fluoroquinolones, tetracyclines, proton pump inhibitors, thyroid hormones, sertraline, Vitamin D, warfarin, acetylsalicylic acid) do not affect the efficacy of Fexeric with respect to its ability to lower serum phosphorus.

Effects of Fexeric on other medicinal products

Since citrate is known to increase aluminium absorption, aluminium-based compounds should be avoided while patients receive Fexeric.

Treatment with Fexeric may lead to elevations in iron stores, particularly in patients receiving concomitant intravenous iron therapy. Patients with elevated ferritin levels receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Reductions in ESA use with Fexeric have been observed. Therefore, patients may need a reduction in the dose of ESAs.

In drug-drug interaction studies in healthy male and female subjects, Fexeric decreased the bioavailability of concomitantly administered ciprofloxacin (as measured by the area under the curve [AUC]) by approximately 45%. However, there was no interaction when Fexeric and ciprofloxacin were taken 2 hours apart. Consequently, ciprofloxacin should not be taken at the same time, but at least 2 hours before or after Fexeric. Fexeric did not alter the bioavailability of the following medicinal products when concomitantly administered: clopidogrel, digoxin, diltiazem, glimepiride, losartan.

From in vitro studies, certain antibiotic (doxycycline, cefdinir), anticonvulsant (valproate sodium), antidepressant (sertraline HCl), bisphosphonate (alendronate sodium), anti-parkinsonian (levodopa)

and immunosuppressant (methotrexate) medications showed the potential to interact with Fexeric: any of these or other medicinal products that have the potential to interact with Fexeric, should be taken at least 2 hours before or after Fexeric.

Since iron-based preparations are known to reduce the absorption of levothyroxine (thyroxine), physicians should consider monitoring suitable markers or clinical signs of efficacy if these medicinal products are concomitantly administered with Fexeric.

Although the potential for interactions with medicinal products seems low, for concomitant treatment with products with a narrow therapeutic window, the clinical effect/adverse events should be monitored on initiation or dose adjustment of Fexeric or the concomitant product.

4.6 Fertility, pregnancy and lactation

Pregnancy and women of childbearing potential

There are no data regarding the use of ferric citrate coordination complex in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Fexeric is not recommended during pregnancy and in women of childbearing potential not using contraceptive methods.

Breast-feeding

It is not known whether ferric citrate coordination complex/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fexeric therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available on the potential influence of Fexeric on fertility.

4.7 Effects on ability to drive and use machines

Fexeric has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in dialysis-dependent chronic kidney disease (CKD 5D) patients during treatment were discoloured faeces and diarrhoea occurring in 18% and 13% of patients, respectively. These adverse reactions are characteristic of iron-containing medicinal products and abated with time with continued dosing. All serious adverse reactions were gastrointestinal in nature (abdominal pain, constipation, diarrhoea, gastritis, gastritis erosive, and haematemesis). These serious adverse reactions were uncommon (less than 1 case of each per 100 patients) and were each reported in 0.2% (1/557) of CKD 5D patients who received Fexeric.

The most commonly reported adverse reactions in non-dialysis dependent CKD (CKD ND) patients during treatment were discoloured faeces, constipation and diarrhoea occurring in 27%, 13% and 11% of patients, respectively. None of the reported serious events in Study 204 were considered to be possibly related to Fexeric. In the remaining non-dialysis studies, a total of 3 serious adverse reactions reported in 2 patients were gastrointestinal in nature (gastrointestinal ulcer, gastric polyps and colonic polyps).

Increases in ferritin and TSAT above safety thresholds are observed with Fexeric use.

Tabulated list of adverse reactions

The safety of Fexeric for the treatment of hyperphosphataemia has been investigated in 18 clinical trials involving a total of 1388 CKD 5D patients with treatment duration of up to 2 years and 145 CKD ND patients with treatment duration of 12 weeks to 1 year.

In CKD 5D patients, the primary evaluation of safety is based on the integrated analysis of data from 4 studies involving 557 CKD 5D patients treated with Fexeric for up to 1 year. In CKD ND patients, the primary evaluation of safety is based on data from the pivotal study (Study 204), where 75 patients were treated with Fexeric for 12 weeks. Adverse reactions reported in CKD 5D and CKD ND patients are presented in Tables 1 and 2, respectively. Frequencies of adverse reactions are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000).

Table 1: Adverse reactions observed during clinical studies in which Fexeric was administered in CKD 5D patients on haemodialysis or peritoneal dialysis.

System organ class by MedDRA	**Adverse Reaction**
Infections and Infestations	
Uncommon:	Bronchitis
Metabolism and nutrition disorders	
Uncommon:	Decreased appetite, hyperkalaemia, hypophosphataemia, increased appetite
Nervous system disorders	
Uncommon:	Dizziness, headache
Cardiac disorders	
Uncommon:	Palpitations, dyspnoea
Vascular disorders	
Uncommon:	Malignant hypertension
Respiratory, Thoracic and Mediastinal disorders	
Uncommon:	Pulmonary oedema, wheezing
Gastrointestinal disorders	
Very common:	Diarrhoea, discoloured faeces
Common:	Abdominal pain/discomfort/distension, constipation, nausea, vomiting
Uncommon:	Abnormal faeces, bowel movement irregularity, dry mouth, dysgeusia, dyspepsia, flatulence, frequent bowel movements, gastritis, gastritis erosive, gastrooesophageal reflux disease, haematemesis, peptic ulcer
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, rash
Renal and urinary disorders	
Uncommon:	Incontinence
General disorders and administration site conditions	
Uncommon:	Pain, thirst
Investigations	
Uncommon:	Abnormal breath sounds, increased serum ferritin, increased transferrin saturation, increased weight
Injury, Poisoning and Procedural Complications	
Uncommon:	Muscle injury

Table 2: Adverse reactions observed during clinical studies in which Fexeric was administered in CKD ND patients.

System Organ Class by MedDRA	Adverse Reaction
Metabolism and nutrition disorders	
Common:	Hypophosphataemia
Gastrointestinal disorders	
Very common:	Diarrhoea, constipation, discoloured faeces
Common:	abdominal pain/discomfort, nausea, vomiting, haemorrhoids, haematochezia, mucous stools, dyspepsia, flatulence, dry mouth

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data are available regarding overdose of Fexeric in humans. In patients with CKD, the maximum dose studied was 12 g (12 tablets) of Fexeric per day.

Iron overdose is dangerous, particularly in children, and requires immediate attention. The symptoms of acute iron overdose include vomiting, diarrhoea, abdominal pain, irritability, and drowsiness. If someone is known or suspected to have accidentally or intentionally ingested an overdose of Fexeric, immediate medical attention should be sought.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalemia and hyperphosphatemia
ATC code: V03AE08

Mechanism of action

This medicine contains ferric citrate coordination complex as the active substance. The iron component reacts with dietary phosphate in the gastrointestinal (GI) tract and precipitates phosphate as ferric phosphate. This compound is insoluble and is excreted in the stool, reducing the amount of phosphate that is absorbed from the GI tract. By binding phosphate in the GI tract and decreasing absorption, Fexeric lowers the levels of serum phosphorus. Following absorption, citrate is converted into bicarbonate by the tissues.

Clinical efficacy

The ability of Fexeric to control serum phosphorus in CKD patients was principally evaluated in one long-term, pivotal Phase III trial (Study 304) in CKD 5D patients, and in one pivotal Phase II, 12 week, placebo-controlled trial (Study 204) in CKD ND patients with anaemia. Both studies were performed in North American and/or Asian patients.
As a secondary endpoint in dialysis patients, and a co-primary endpoint in non-dialysis patients, the ability of Fexeric to increase iron stores was also evaluated.

Effects on phosphorus homeostasis

In the pivotal dialysis study 304, following a 2-week washout period, 441 CKD 5D patients with hyperphosphatemia were randomised to receive Fexeric (n=292) or active control (sevelamer carbonate and/or calcium acetate; n=149) open-label for 52 weeks. The starting dose of Fexeric was 6 tablets/day (6 g/day), in divided doses with meals. The starting dose of active control was the patient's dose prior to the washout period.

The dose of phosphate binder was titrated as needed to maintain serum phosphorus levels between 3.5 and 5.5 mg/dl, to a maximum of 12 g/day. Non-inferiority to sevelamer carbonate was determined at Week 12. Following completion of the 52-week active-controlled period, patients were eligible to enter a 4-week placebo-controlled period in which they were re-randomized to receive Fexeric (n=96) or placebo (n=96).

After 12 weeks of treatment, the mean (± SD) change in serum phosphorus from baseline was −2.02 ± 2.0 mg/dl for Fexeric and −2.21 ± 2.18 mg/dl for sevelamer carbonate, demonstrating non-inferiority of Fexeric to sevelamer. During the overall 52-week active-controlled period, the decrease in serum phosphorus (approximately 2.0 mg/dl following up to a 2 week washout period) and the percentage of patients who achieved and maintained serum phosphorus ≤ 5.5 mg/dl (approximately 62%) were comparable in both the Fexeric and the active control groups (Table 3). During the subsequent 4-week placebo-controlled period, the serum phosphorus levels remained stable in patients receiving Fexeric (mean decrease of 0.24 mg/dl), whereas patients receiving placebo had a mean increase of 1.79 mg/dl ($p < 0.0001$ for treatment difference).

In the pivotal non-dialysis study 204, a total of 148 CKD ND patients with hyperphosphatemia and iron deficiency anaemia received treatment with study drug; there were 141 patients in the intent-to-treat population (Fexeric: 72 patients; Placebo: 69 patients). The starting dose of Fexeric was 3 tablets a day (3 g/day) in divided doses with meals and was adjusted as needed to a maximum of 12 g/day in order to maintain serum phosphorus levels between 3.0 and 3.5 mg/dl.

During the 12-week treatment period, patients treated with Fexeric had a significant decrease in serum phosphorus, compared to the placebo group ($p < 0.001$ for treatment difference) (Table 3). Urinary phosphorus excretion and FGF-23 were also significantly decreased relative to baseline in the CKD ND patients treated with Fexeric compared to patients treated with placebo.

Table 3: Summary of efficacy parameters on phosphorus homeostasis at Week 12 and Week 52 in Study 304 (CKD 5D) and at Week 12 in Study 204 (CKD ND)

	Study 304 (CKD 5D)		**Study 204 (CKD ND)**	
Parameter	**Fexeric N=281**	**Active Control N=146**	**Fexeric N=72**	**Placebo N=69**
Baseline serum phosphorus (mean ± SD, mg/dl)	7.41 ± 1.6	7.56 ± 1.7	4.5 ± 0.61	4.7 ± 0.60
Serum phosphorus change from baseline at Week 12[§] (mean ± SD, mg/dl)	−2.02 ± 2.0	−2.22 ± 2.1 (−2.21 ± 2.2 for sevelamer only)	−0.7 ± 0.61	−0.3 ± 0.74
Serum phosphorus change from baseline at Week 52 (mean ± SD, mg/dl)	−2.03 ± 2.0	−2.18 ± 2.3	NAP	

Parameter	Study 304 (CKD 5D)		Study 204 (CKD ND)	
	Fexeric N=281	**Active Control N=146**	**Fexeric N=72**	**Placebo N=69**
Proportion of serum phosphorus responders at Week 12 (%)	60.9*	63.7*	69.4**	27.5**
Proportion of serum phosphorus responders at Week 52 (%)	62.3*	63.0*	NAP	

[§] Primary endpoint in Study 304; Co-primary endpoint in Study 204.
*Proportion of patients achieving serum phosphorus ≤ 5.5 mg/dl in CKD 5D patients;
**Proportion of patients achieving serum phosphorus ≤ 4.0 mg/dl in CKD ND patients
NAP: not applicable; SD: standard deviation

Effects on iron homeostasis

In the pivotal dialysis study 304, CKD 5D patients treated with Fexeric, compared with patients treated with active control, had significantly higher increases in ferritin and TSAT levels after 52 weeks of treatment (Table 4), and significantly lower cumulative intravenous iron (96 versus 149 mg/month) and ESA use (7,713 versus 9,183 IU/week) during the same period. During the 52-week treatment period, haemoglobin remained relatively stable in the Fexeric group compared to the active control group (Table 4).

In the pivotal non-dialysis study 204 CKD ND patients treated with Fexeric had a significant increase in serum TSAT, ferritin and haemoglobin levels compared to the placebo group after 12 weeks of treatment ($p < 0.001$ for treatment difference for each parameter) (Table 4).

Table 4: Summary of results on iron homeostasis at Week 12 and Week 52 in Study 304 (CKD 5D) and at Week 12 in Study 204 (CKD ND)

Parameter	Study 304 (CKD 5D)		Study 204 (CKD ND)	
	Fexeric N=281	**Active Control N=146**	**Fexeric N=72**	**Placebo N=69**
Baseline TSAT (mean ± SD, %)	31.3 ± 11.2	30.8 ± 11.6	21.6 ± 7.4	21.0 ± 8.3
TSAT change from baseline at Week 12[§] (mean ± SD, %)	8.8 ± 18.3	0.5 ±15.8	10.2 ± 12.5	−1.0 ± 7.0
TSAT change from baseline at Week 52 (mean ± SD, %)	7.9 ± 18.3	−1.0 ± 14.9	NAP	
Baseline ferritin (mean ± SD, ng/ml)	592.8 ± 292.9	609.5 ± 307.7	115.8 ± 83.1	110 ± 80.9
Ferritin change from baseline at Week 12 (mean ± SD, ng/ml)	162.7 ± 284.3	44.0 ± 270.4	73.5 ± 76.2	−4.4 ± 47.5
Ferritin change from baseline at Week 52 (mean ± SD, ng/ml)	302.1 ± 433.7	22.4 ± 374.0	NAP	

Parameter	Study 304 (CKD 5D)		Study 204 (CKD ND)	
	Fexeric N=281	**Active Control N=146**	**Fexeric N=72**	**Placebo N=69**
Proportion with ferritin > 500 ng/ml at baseline	166 (59.1%)	87 (59.6%)	0	0
Proportion with ferritin > 500 ng/ml at Week 12	174 (61.9%)	86 (58.9%)	3 (4.2%)	0
Proportion with ferritin > 500 ng/ml at Week 52	160 (56.9%)	63 (43.2%)	NAP	
Baseline Hgb (mean ± SD, g/dl)	11.61 ± 1.24	11.71 ± 1.26	10.5 ± 0.81	10.6 ± 1.1
Hgb change from baseline at Week 12 (mean ± SD, g/dl)	0.19 ± 1.41	−0.19 ± 1.53	0.4 ± 0.75	−0.2 ± 0.91
Hgb change from baseline at Week 52 (mean ± SD, g/dl)	−0.20 ± 1.34	−0.55 ± 1.59	NAP	

[§] Co-primary endpoint in Study 204.
All other parameters were secondary or exploratory endpoints in the two studies.
Hgb: haemoglobin; NAP: not applicable; SD: standard deviation; TSAT: transferrin saturation

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fexeric in in one or more subsets of the paediatric population in the treatment of hyperphosphataemia related to chronic kidney disease (see section 4.2 for information on paediatric use).

Hepatic impairment

Of the 557 patients receiving Fexeric in the pooled safety population, there were 67 (12%) patients with evidence of liver dysfunction at baseline. These patients were treated according to the recommended dosing regimen without any safety concerns.
There was no evidence of hepatic impairment or significant alteration of hepatic enzymes across the clinical studies with Fexeric, including the long-term studies.

5.2 Pharmacokinetic properties

Formal pharmacokinetic studies have not been performed due to the medicine's predominantly localised primary mechanism of action in the GI tract.
Examination of serum iron storage parameters has shown that there is low systemic absorption of iron of approximately 1% from Fexeric.

5.3 Preclinical safety data

The non clinical programme was based on 7 repeat dose toxicology studies in rats and dogs. The target organ for primary toxicity of ferric citrate is the GI tract, with evidence of mucosal erosion and acute to sub-acute inflammation of the GI tract in dogs at elevated doses. In iron replete dogs, microscopic and macroscopic findings in the liver were consistent with signs of iron accumulation.

Data on primary and secondary pharmacodynamics, safety pharmacology and pharmacokinetics of Fexeric were derived from the repeat dose toxicology studies, and did not reveal safety concerns for humans.

Information on genotoxicity, carcinogenic potential, toxicity to reproduction and development of ferric citrate was bridged from scientific literature. Data from carcinogenicity studies have shown that ferric citrate is not carcinogenic in mice and rats when administered intramuscularly or subcutaneously. Ferric citrate was neither mutagenic in the bacterial reverse mutation assay (Ames test) nor clastogenic in the chromosomal aberration test in Chinese hamster fibroblasts.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Starch, pregelatinised
Calcium stearate

Film-coating
Hypromellose
Titanium Dioxide
Triacetin
Sunset Yellow FCF (E110)
Allura Red AC (E129)
Indigo Carmine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
Shelf-life after first opening of the bottle: 60 days

6.4 Special precautions for storage

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with child-resistant closure with desiccant.
Pack size: 200 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Akebia Europe Limited
c/o Matheson
70 Sir John Rogerson's Quay
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1039/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 September 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Propak Health Ltd
3-4 Ballyboggan Industrial Estate
Ballyboggan Road
Finglas
Dublin 11
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): prospective, observational, multicentre study in CKD patients treated with Fexeric in order to gain long-term (2 years) safety data (including iron overload events, infective and gastrointestinal events) particularly in EU patients, elderly and very elderly patients, dialysed (HD, PD) and non-dialysed patients, and in addition reflecting the specific risks in subgroups of serum ferritin levels > 500 ng/ml and in patients in the range 200 to < 500 ng/ml.	54 months after first launch in EU

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Fexeric 1 g film-coated tablets
ferric citrate coordination complex

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 g of ferric citrate coordination complex (equivalent to 210 mg of ferric iron).

3. LIST OF EXCIPIENTS

Also contains sunset yellow FCF (E110), Allura Red AC (E129), see the package leaflet for futher information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film coated tablet
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after first opening of the bottle: 60 days
Open date: (Bottle only)

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Akebia Europe Limited
c/o Matheson
70 Sir John Rogerson's Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1039/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fexeric 1 g (carton only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Fexeric 1 g film-coated tablets
ferric citrate coordination complex

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fexeric is and what it is used for

Fexeric contains ferric citrate coordination complex as the active ingredient. In adults with impaired kidney function it is used to lower high blood phosphorus levels.

Phosphorus is contained in many foods. Patients with kidneys that do not work properly are not able to eliminate phosphorus from their body adequately. This can lead to high phosphorus levels in the blood. Keeping the phosphorus level normal is important to maintain healthy bones and blood vessels and to prevent itchy skin, red eyes, bone pain or bone fractures.

Fexeric binds to the phosphorus from food in your digestive tract to prevent it from being absorbed into your blood. The Fexeric-bound phosphorus is then excreted from your body in faeces.

You may have been advised to follow a special diet to prevent the phosphorus in your blood rising to high levels. If this is the case, you must continue to follow the special diet even if you are taking Fexeric.

2. What you need to know before you take Fexeric

Do not take Fexeric
- if you are allergic to ferric citrate coordination complex or any of the other ingredients of this medicine (listed in section 6)
- if you have low levels of phosphorus in your blood
- if you have a severe stomach or bowel disease such as stomach or bowel bleeding

- if you have haemochromatosis, a condition causing the body to absorb too much iron from the diet
- if you have any other disorder associated with too much iron

Warnings and precautions
Talk to your doctor or pharmacist before taking Fexeric if you have:
- too much iron in your body
- bowel inflammation

Monitoring tests
Fexeric increases iron levels in your body. Because too much iron is unsafe, your blood will be tested at regular intervals to check iron levels. This blood test may be part of your routine tests for your kidney disease.

Children and adolescents
Do not give this medicine to children and adolescents below the age of 18 years. The safety and effectiveness of Fexeric have not been studied in this population.

Other medicines and Fexeric
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following medicines can affect or be affected by Fexeric:
- other iron-containing medicines
  Fexeric contains iron and your doctor may need to adjust the dose of your other iron-containing medicines.
- aluminium containing medicines
  Fexeric should not be taken at the same time as aluminium containing medicines.
- Also tell your doctor or pharmacist if you are taking or might take the medicines below. Your doctor may want to change the dose of these medicines or advise you to take these medicines 2 hours before or after Fexeric. Monitoring blood levels of these medicines may also be considered:
  - ciprofloxacin, doxycycline, cefdinir: medicines to treat bacterial infections
  - valproic acid: a medicine to treat epilepsy and mental disorders
  - sertraline: a medicine to treat depression
  - methotrexate: a medicine to treat rheumatoid arthritis, 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

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- **pregnancy**

If you are able to become pregnant, you must use birth control during treatment. If you become pregnant during treatment, you must ask your doctor for advice. It is unknown whether Fexeric has any effect on unborn babies.

- **breast-feeding**

Tell your doctor if you wish to breast-feed your baby. It is unknown whether Fexeric may pass through breast milk and affect your baby.

Driving and using machines
Fexeric has no influence on your ability to drive and use machines.

Fexeric contains sunset yellow FCF (E110) and Allura Red AC (E129)
These may cause allergic reactions.

3. How to take Fexeric

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

- **starting** dose for adults: 3 to 6 tablets daily, in separated doses, with or immediately after main meals of the day. Taking the tablets with meals will help the medicine to work.

Patients not on dialysis require the lower starting dose: 3 tablets daily, in separated doses, with or immediately after meals of the day.

Your doctor may decrease or increase the starting dose depending on the level of phosphorus in your blood. Your doctor will monitor the phosphorus levels regularly. This blood test may be part of your routine tests for your kidney disease.

- **maximum** dose: 12 tablets daily, in separated doses, with or immediately after meals of the day.

Method of use
Take the tablets whole, with one glass of water, with or immediately after meals.

If you take more Fexeric than you should
If you take too much Fexeric, tell your doctor of pharmacist.
Contact a doctor or poison control centre immediately if a child accidentally takes Fexeric.

If you forget to take Fexeric
Take the next dose at the usual time with a meal. Do not take a double dose to make up for a forgotten dose.

If you stop taking Fexeric
Treatment of high blood phosphorus levels is usually required for a long period of time. It is important that you continue taking Fexeric for as long as your doctor prescribes the medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:
- severe abdominal pain or constipation (uncommon)
- vomiting of blood (uncommon)
- blood in the stools (uncommon)

The following side effects have been reported with Fexeric in dialysis patients:

Very common side effects (may affect more than 1 in 10 people):
- discoloured stools
- diarrhoea

Common side effects (may affect up to 1 in 10 people):
- constipation
- abdominal pain/discomfort
- abdominal distension or bloating
- nausea, vomiting

Uncommon side effects (may affect up to 1 in 100 people):
- changes in iron blood test results
- decreased or increased appetite
- indigestion, flatulence
- inflammation of stomach lining, ulcer of mucosal lining of the stomach or the first part of the bowel
- reflux of stomach juices in the oesophagus
- abnormal stools, irregularity in bowel movement
- low serum phosphorus levels
- dry mouth
- taste disturbance
- headache
- dizziness
- low serum potassium levels
- incontinence
- skin rash, itching
- palpitations
- shortness of breath, wheezing, abnormal breath sounds
- pain
- thirst
- bronchitis
- muscle injury
- increased weight
- fluid in the lungs
- very high blood pressure

The most common side effects (affecting more than 1 in 10 people) in patients not on dialysis also concern the stomach or bowel:
- discoloured stools
- diarrhoea
- constipation

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fexeric

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after "EXP". The expiry date refers to the last day of that month.

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.
After first opening of the bottle, use within 60 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fexeric contains
The active substance is ferric citrate coordination complex.
Each film-coated tablet contains 1 g of ferric citrate coordination complex (equivalent to 210 mg of ferric iron).
The other ingredients are pregelatinised starch, calcium stearate, hypromellose, titanium dioxide, triacetin, sunset yellow FCF (E110), allura red AC (E129), indigo carmine.

What Fexeric looks like and contents of the pack
Fexeric film-coated tablets are peach-coloured, oval-shaped tablets embossed with "KX52" on one side. Tablets are 19 mm long, 7.2 mm thick and 10 mm wide.

The tablets are packed in plastic bottles with child-resistant caps. They are supplied in one pack size of 200 tablets per bottle.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Akebia Europe Limited
c/o Matheson
70 Sir John Rogerson's Quay
Dublin 2
Ireland

Manufacturer:
Propak Health Ltd.
3-4 Ballyboggan Industrial Estate
Ballyboggan Road
Finglas
Dublin 11
Ireland

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.