ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xoanacyl 1 g film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 g of ferric citrate (as coordination complex, containing 210 mg of ferric iron).

Excipients with known effect

Each film-coated tablet contains 0.99 mg sunset yellow FCF (E110) and 0.70 mg allura red AC (E129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Peach-coloured, oval shaped, (19 mm long, 7.2 mm thick and 10 mm wide) embossed with “KX52” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xoanacyl is indicated for the treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with chronic kidney disease (CKD).

4.2 Posology and method of administration

Posology

Treatment should be initiated under the supervision of a physician experienced in the management of patients with renal disorders.

Starting dose

The recommended starting dose of Xoanacyl is:

- Non-dialysis dependent CKD patients: 3 g a day
- Dialysis dependent CKD patients not already receiving a phosphate binder: 3-6 g a day based on iron parameters and serum phosphorus levels
- Dialysis dependent CKD patients already receiving a phosphate binder and switching to Xoanacyl: 6 g a day

Xoanacyl must be taken with or immediately after meals. The total daily dose should be equally divided across the meals of the day where possible, rounded to the nearest whole film-coated tablet; if total daily dose cannot be divided equally, the higher number of film-coated tablets should be taken with the largest meal of the day.

The efficacy of Xoanacyl has not been studied in clinical trials in dialysis dependent patients without permitting concomitant treatment with intravenous iron and/or erythropoiesis-stimulating agent (ESA) as needed.

Other oral iron therapy and phosphate binding therapy should be discontinued on initiation of Xoanacyl. A reduction or discontinuation of intravenous iron may also be required (see section 4.4).

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

Dose titration

Iron parameters (e.g. haemoglobin, serum ferritin and transferrin saturation (TSAT)) and serum phosphorus concentrations should be monitored within 2 to 4 weeks of starting or changing the dose of Xoanacyl, and approximately every 2-3 months when stable. The dose can be increased or decreased by 1 to 2 film-coated tablets per day at 2- to 4-week intervals as needed to maintain iron parameters and serum phosphorus at recommended target levels up to a maximum of 12 film-coated tablets per day. Consideration should be given to the dual effect of the product to avoid overtreatment (see section 4.4).

There are limited data available for doses higher than 9 film-coated tablets per day in CKD patients not on dialysis; therefore, in non-dialysis dependent CKD patients doses higher than 9 film-coated tablets per day should not be used unless with intensified monitoring.

Treatment should be temporary discontinued if hypophosphatemia develops or if serum ferritin exceeds 700 ng/mL and/or TSAT exceeds 40%. Once resolved, treatment could be resumed at a lower dose level (see section 4.4).

If an intake is missed during the day, patients should be instructed not to take the forgotten dose at the next meal.

Special populations

Elderly population

No dose adjustment is necessary in elderly (see section 5.1).

Hepatic impairment

Patients with hepatic impairment should initiate treatment with the lower starting dose, 3 film-coated tablets per day.

Paediatric population

The safety and efficacy of Xoanacyl in children and adolescents below 18 years have not yet been established. No data are available.

Method of administration

For oral use.

The film-coated tablets must be swallowed whole; film-coated tablets must not be chewed or crushed because it may cause discoloration of mouth and teeth.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;

- Active severe gastrointestinal disorders;
- Haemochromatosis and any other iron accumulation disorders.

4.4 Special warnings and precautions for use

Monitoring iron parameters

All patients receiving this medicinal product require at least quarterly monitoring of serum iron storage parameters (serum ferritin and TSAT) to ensure sufficient effect and to avoid iron overload which may have negative health consequences, such as decreased bone mineral density.

Xoanacyl should be temporarily discontinued if serum ferritin is above 700 ng/mL and/or TSAT is above 40%. In this situation, the strategy for iron supplementation (including, if applicable, concomitant intravenous iron) should be revised.

Concomitant treatment with intravenous iron and ESA may be needed, especially in dialysis dependent patients. Doses should be carefully selected to achieve appropriate levels of haemoglobin taking into account the targets recommended for such products. The need for intravenous iron and ESA may vary over time.

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 Xoanacyl should not receive concomitant treatment with other oral iron preparations.

Monitoring serum phosphorous levels

All patients receiving this medicinal product require at least quarterly monitoring of serum phosphorous. Xoanacyl should be temporary discontinued if hypophosphataemia develops (see section 4.8).

Patients treated with Xoanacyl should not receive concomitant treatment with other phosphate binders.

Inflammatory bowel disease and gastrointestinal bleeding

Xoanacyl is contraindicated in patients with active severe gastrointestinal disorders (see section 4.3). Patients with active, symptomatic inflammatory bowel disease and recent symptomatic gastrointestinal bleeding were excluded from clinical studies. Xoanacyl should only be used in these patients following careful assessment of benefit/risk and monitoring of gastrointestinal symptoms following initiation of treatment should occur with discontinuation in case of exacerbation.

Gastrointestinal disturbances

Gastrointestinal adverse reactions have been reported including severe cases of diarrhoea, abdominal pain and nausea and their occurrence should be monitored (see section 4.8).
Xoanacyl must be discontinued in patients with active severe gastrointestinal disorders (see section 4.3).

Excipients with known effect

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Since citrate is known to increase aluminium absorption, aluminium-based compounds (e.g. antacids containing aluminium hydroxide) should be avoided while patients receive Xoanacyl.

Medicinal products with special recommendations for concomitant use with Xoanacyl

Medicinal products that may act on iron absorption in the gastrointestinal (GI) tract

The following medicinal products have the potential to interact with Xoanacyl and should not be taken at the same time, but at least 2 hours before or after Xoanacyl:

- Calcium supplements;
- Calcium based and magnesium based antacids (e.g. containing oxides, hydroxides or salts of magnesium and calcium);

Medicinal products that may interact with Xoanacyl

The following medicinal products have the potential to interact with Xoanacyl and should not be taken at the same time, but at least 2 hours before or after Xoanacyl:

- Levothyroxine (thyroxine). Since iron-based preparations are known to reduce the absorption of levothyroxine a reduction in levothyroxine availability could occur. Thyroid function should be monitored, in particular after initiation and dose adjustments of Xoanacyl. Levothyroxine dose may need to be adjusted during treatment with Xoanacyl.
- Certain antiparkinsonian treatments (levodopa, benserazide, entacapone);
- Captopril (angiotensin-converting enzyme inhibitor with sulfhydryl group);
- Iron chelating agents (e.g. penicillamine);
- Biphosphonates (e.g. alendronate sodium);
- Methyldopa (alpha-2-adrenergic receptor agonist);
- Certain antibiotics: tetracyclines (e.g. doxycycline), cefdinir, fluoroquinolones (e.g. ciprofloxacin, levofloxacin). In drug-drug interaction studies in healthy male and female subjects, Xoanacyl 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 Xoanacyl and ciprofloxacin were taken 2 hours apart.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of ferric citrate coordination complex in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Xoanacyl is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown 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 Xoanacyl 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 Xoanacyl on fertility.

4.7 Effects on ability to drive and use machines

Xoanacyl has no or negligible 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 CKD patients treated with Xoanacyl were diarrhoea and faeces discoloured which occurred in 20.2% and 19.5% of patients, respectively.

Tabulated list of adverse reactions

Adverse reactions reported based on clinical studies in CKD patients (N=858) are presented in Table 1. The adverse reactions are listed by SOC (system organ class) and by frequency, most frequent adverse reaction first. 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); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse reactions observed during clinical studies in which Xoanacyl was administered to CKD patients.

MedDRA System Organ Class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders			Hypophosphataemia	Iron overload
Gastrointestinal disorders	Diarrhoea, discoloured faeces	Abdominal pain /discomfort/distension, nausea, constipation, dyspepsia, flatulence	Haematochezia, haemorrhoids	

Description of selected adverse reactions

Gastrointestinal tract disturbances

The most common adverse events occurred in the System Organ Class Gastrointestinal disorders (42.1%), including severe cases (2.7%) and cases that led to drug discontinuation (5.9%). Severe gastrointestinal adverse reactions included diarrhoea (1.3%), abdominal pain (0.6%) and nausea (0.1%). Gastrointestinal adverse reactions resulting in discontinuation were most frequently reported due to diarrhoea (3.4%).

Iron overload

Increases in ferritin and TSAT above safety thresholds have been observed with Xoanacyl use (see section 4.4).

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

Iron overdose is dangerous 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 Xoanacyl, immediate medical attention should be sought. Supportive and symptomatic measures reflecting best standard medical care should be implemented and the use of an iron chelator such desferrioxamine should be considered.

Xoanacyl overdose can also induce hypophosphataemia that could lead to nausea and headache and should be treated by standard clinical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products; drugs for treatment of hyperkalaemia and hyperphosphataemia, ATC code: V03AE08

Mechanism of action

This medicinal product contains ferric citrate coordination complex as the active substance, specifically designed to have a high surface area and a defined molar ratio of ferric iron to citrate. The high surface area of ferric citrate coordination complex impacts ferric iron solubility at physiological pH and allows part of ferric iron to be absorbed and supply iron to the metabolic pathway.

Ferric citrate coordination complex has a dual mechanism of action, one that is associated with providing a source of ferric iron and one associated with decreasing the absorption of phosphorous. The dual mechanism of action result in a direct impact on reducing functionally active intact fibroblast growth factor 23 (iFGF-23).

Following oral administration, soluble ferric iron is reduced from the ferric to the ferrous form by ferric reductase in the gastrointestinal (GI) tract. After transport through the enterocytes into the blood, oxidized ferric iron circulates bound to the plasma protein transferrin, and can be incorporated into haemoglobin.

The non-absorbed part of the complex reacts with dietary phosphate in the GI tract and precipitates phosphate as ferric citrate phosphate complex. 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, ferric citrate coordination complex lowers the levels of serum phosphorus. Following absorption, citrate is converted into bicarbonate by the tissues.

Clinical efficacy

Three pivotal clinical studies have been conducted to support the efficacy of ferric citrate coordination complex in the treatment of concomitant iron deficiency and elevated serum phosphorous in adult chronic kidney disease (CKD) patients. Two studies were in non-dialysis dependent (NDD) CKD patients and one study was in dialysis dependent (DD) CKD patients.

Study 1 (KRX-0502-204)

A total of 149 NDD CKD subjects with iron deficiency anaemia (haemoglobin > 9.0 and < 12.0 g/dL [> 5.6 and < 7.5 mmol/L], serum ferritin ≤ 300 ng/mL, transferrin saturation [TSAT] ≤ 30%, serum ferritin ≤ 300 ng/mL) and elevated serum phosphorous (≥ 4 and < 6 mg/dL [≥ 1.3 and < 1.9 mmol/L]) were randomised to receive either ferric citrate coordination complex (N=75) or placebo (N=74). The starting dose was 3 film-coated tablets/day which was titrated based on serum phosphorous levels; the maximum dose was 12 film-coated tablets/day.

The co-primary efficacy endpoint was change from baseline to Week 12 in TSAT and change from baseline to Week 12 in serum phosphorous. Key secondary efficacy endpoints included change from baseline to Week 12 in serum ferritin, haemoglobin and intact fibroblast growth factor-23 (iFGF-23).

At enrolment into the study 20.3%, 52.7% and 25.7% of subjects had Stage 3, 4 and 5 CKD, respectively. The mean age of subjects was 65.1 years (range 21 to 88 years; 56.1% ≥ 65 years) with the majority being Caucasian (77.7%) and female (64.9%). The mean daily dose of ferric citrate coordination complex was 5.1 film-coated tablets/day.

Primary and secondary endpoints relating to iron and phosphorous homeostasis are summarised in table 2.

Table 2: Study 1 - Summary of results from primary and key secondary endpoints

Parameter		**Placebo (N=69)**	**Ferric citrate coordination complex (N=72)**
Serum TSAT, %	**Baseline**		
	Mean (SD)	21.0 (8.26)	21.6 (7.44)
	Week 12, change from baseline		
	LS mean (SE)	-1.1 (1.20)	10.2 (1.18)
	Difference to placebo (SE)	-	11.3 (1.70)
	95% CI for difference		8.0, 14.7
	p-value	-	< 0.001[a]
Serum phosphorous, mg/dL [a]	**Baseline,**		
	Mean (SD)	4.7 (0.60)	4.5 (0.61)
	Week 12, change from baseline		
	LS mean (SE)	-0.2 (0.07)	-0.7 (0.07)
	Difference to placebo (SE)	-	-0.5 (0.10)
	95% CI for difference		-0.7, -0.3
	p-value	-	< 0.001[a]
Serum ferritin, ng/mL	**Baseline**		
	Mean (SD)	110.0 (80.88)	115.8 (83.11)
	Week 12, change from baseline		
	LS mean (SE)	-4.2 (7.67)	73.3 (7.51)
	Difference to placebo (SE)	-	77.5 (10.83)
	95% CI for difference		56.2, 98.7
	p-value	-	< 0.001[a]
Haemoglobin, g/dL [b]	**Baseline**		
	Mean (SD)	10.6 (1.07)	10.5 (0.81)
	Week 12, change from baseline		
	LS mean (SE)	-0.2 (0.10)	0.4 (0.10)
	Difference to placebo (SE)	-	0.6 (0.14)
	95% CI of difference to placebo		0.4, 0.9
	p-value	-	< 0.001[a]
iFGF-23, pg/mL	**Baseline**		
	Mean (SD)	263.2 (226.30)	319.0 (577.48)
	Week 12, change from baseline		
	LS mean (SE)	17.4 (37.10)	-108 (36.21)

	Difference to placebo (SE) 95% CI for difference p-value	- -	-125 (52.42) -220, -21.7 0.017 [c]

A sequential hierarchal testing strategy was used for the primary and secondary efficacy endpoints.
CI=confidence interval; iFGF-23=intact fibroblast growth factor-23; SD=standard deviation; SE=standard error; TSAT=transferrin saturation.
[a] values can be estimated to mmol/L using conversion factor of 0.3229; [b] values can be estimated to mmol/L using conversion factor of 0.6206; [c] ANCOVA model with treatment as a fixed effect and baseline value as the covariate.

Study 2 (KRX-0502-306)

Subjects with NDD CKD and iron deficiency anaemia (haemoglobin ≥ 9.0 and ≤ 11.5 g/dL [≥ 5.6 and ≤ 7.1 mmol/L], serum ferritin ≤ 200 ng/mL and TSAT ≤ 25%) with serum phosphorous ≥ 3.5 mg/dL [≥ 1.1 mmol/L] were enrolled. A total of 234 subjects were randomised to receive either ferric citrate coordination complex (N=117) or placebo (N=117) for 16 weeks with a starting dose of 3 film-coated tablets/day which was subsequently titrated based on haemoglobin levels with a maximum dose of 12 film-coated tablets/day. At Week 16, subjects could enter an 8-week extension phase where all subjects received ferric citrate coordination complex at 3 film-coated tablets/day which could be titrated based on clinical response.

The primary efficacy endpoint was the percentage of haemoglobin responders, defined as a subject with an increase of ≥ 1.0 g/dL [0.62 mmol/L] at any point during the 16-week placebo-controlled phase. Secondary efficacy endpoints included both iron and phosphorous parameters: change from baseline to Week 16 in haemoglobin, TSAT, serum ferritin, percentage of subjects with sustained haemoglobin response (mean change ≥ 0.75 g/dL [0.47 mmol/L] over any 4-week time period during the 16-week placebo-controlled phase, provided ≥ 1.0 g/dL [0.62 mmol/L] was also attained during this period) and change from baseline to Week 16 in serum phosphorous.

At enrolment into the study 48.1%, 42.1% and 9.9% of subjects had Stage 3, 4 and 5 CKD, respectively. The mean age of subjects was 65.4 years (range 26 to 93 years; 58.8% ≥ 65 years) with the majority being Caucasian (68.7%) and female (63.1%). The mean daily dose of ferric citrate coordination complex was 5.0 film-coated tablets/day.

The primary and secondary endpoints are summarised in the following table.

Table 3: Summary of results from primary and secondary endpoints in Study 2

Parameter		Placebo (N=115)	Ferric citrate coordination complex (N=117)
Haemoglobin responders, %	**During randomised period**		
	% of subjects	19.1	52.1
	Difference to placebo (95% CI)	-	33.0 (21.4, 44.6)
	p-value	-	< 0.001 [c]
Sustained haemoglobin responders, %	**During randomised period**		
	% of subjects	14.8	48.7
	Difference to placebo (95% CI)	-	33.9 (22.8, 45.1)
	p-value	-	< 0.001 [c]
Haemoglobin, g/dL [a]	**Baseline**		
	Mean (SD)	10.38 (0.78)	10.44 (0.73)
	Week 16, change from baseline		
	LS mean (SE)	-0.08 (0.10)	0.75 (0.09)
	Difference to placebo (SE)	-	0.84 (0.13)
	95% CI for difference		0.58, 1.10
	p-value	-	< 0.001 [d]
TSAT, %	**Baseline**		
	Mean (SD)	19.6 (6.63)	20.2 (6.43)
	Week 16, change from baseline		
	LS mean (SE)	-0.6 (1.37)	17.8 (1.37)
	Difference to placebo (SE)	-	18.4 (1.94)
	95% CI for difference		14.6, 22.2
	p-value	-	< 0.001 [d]
Serum ferritin, ng/mL	**Baseline**		
	Mean (SD)	81.7 (58.26)	85.9 (55.74)
	Week 16, change from baseline		
	LS mean (SE)	-7.7 (9.23)	162.6 (9.00)
	Difference to placebo (SE)	-	170.3 (12.89)
	95% CI for difference		144.9, 195.7
	p-value	-	< 0.001 [d]
Serum phosphorous, mg/dL [b]	**Baseline**		
	Mean (SD)	4.12 (0.68)	4.23 (0.91)
	Week 16, change from baseline		
	LS mean (SE)	-0.22 (0.07)	-0.43 (0.06)
	Difference to placebo (SE)	-	-0.21 (0.09)
	95% CI for difference		-0.39, -0.03
	p-value	-	0.020 [d]

A sequential hierarchal testing strategy was used for the primary and secondary efficacy endpoints.
CI=confidence interval; SD=standard deviation; SE=standard error; TSAT=transferrin saturation.
[a] values can be estimated to mmol/L using conversion factor of 0.6206; [b] values can be estimated to mmol/L using conversion factor 0.3229 [c] 2-sided chi-squared test; [d] mixed model repeated measures method with the terms of treatment, baseline value, week post-baseline, and treatment by week post-baseline interactions.

Study 3 (KRX-0502-304)

This study was an open-label active controlled study for 52 weeks followed by a 4-week placebo-controlled phase. Subjects with DD CKD (haemodialysis 3 times a week or peritoneal dialysis) with elevated phosphorous levels (serum phosphorous ≥ 6.0 mg/dL [≥ 1.9 mmol/L] after washout of existing phosphate binder), ferritin < 1000 ng/mL and TSAT < 50% were enrolled. Subjects were randomised (N=441) to receive either ferric citrate coordination complex (N=292) or an active control

(N=149) in a 2:1 ratio. The active control group received calcium acetate, sevelamer carbonate, or a combination of these, which was administered based on the last dose administered prior to the start of the washout, or if not remaining on the same phosphate binder, per the prescribing information at the discretion of the investigator. Subjects could continue to receive intravenous iron and erythropoietin stimulating agents as clinically required. At baseline, there were 61% (265/438) and 82% (359/438) of the study population receiving intravenous iron and erythropoietin stimulating agents, respectively. The ferric citrate coordination complex group was administered 6 film-coated tablets/day and the dose titrated based on the serum phosphorous levels, with a maximum dose of 12 film-coated tablets/day. At the end of the 52-week active controlled phase, subjects who had received ferric citrate coordination complex were randomised to either continue to receive ferric citrate coordination complex or receive placebo for a further 4 weeks.

The mean subject age of the DD CKD subjects in the study was 54.4 years (range 19 to 90 years; 20.5% ≥ 65 years). The majority of subjects were African American/black (53.0%) and male (61.2%). During the 52-week active-controlled period, the mean daily dose of ferric citrate coordination complex was 8.8 film-coated tablets/day.

The primary efficacy endpoint evaluated the change from baseline to Week 12 in serum phosphorus for the ferric citrate coordination complex group compared to subjects who received sevelamer carbonate as a sole agent in the active control arm (N=78). The LS mean (95% CI) was -2.03 mg/dL (-2.21, -1.86) in the ferric citrate coordination complex group compared to -2.17 mg/dL (-2.51, -1.84) in the sevelamer carbonate group; with a LS mean for treatment difference of 0.14 mg/dL (95% CI for difference: -0.24, 0.52). This is approximately equivalent to mean decreases of -0.66 and -0.70 mmol/L in the ferric citrate coordination complex and sevelamer groups, respectively (difference of 0.04 mmol/L).

Secondary efficacy endpoints evaluated the treatment effect of ferric citrate coordination complex relative to the active control arm (all treatments) and were the change from baseline to Week 52 in serum ferritin, TSAT and the cumulative use to Week 52 of intravenous iron and ESA (median daily dose).

In the 4-week placebo-controlled phase, there was an increase in serum phosphorous in the group that was switched to placebo (LS mean [95% CI] from the Week 52 baseline to Week 56 of 1.86 mg/dL [1.57, 2.15]) and a continued decrease in the group that remained on ferric citrate coordination complex (-0.32 mg/dL [-0.61, -0.03]). The LS mean treatment difference was -2.18 (95% CI for difference: -2.59, -1.77), which was significant ($p < 0.0001$).

Results from the secondary endpoints are summarised in the table below.

Table 4: Summary of results from secondary endpoints in Study 3

Parameter		Active control (N=146) [a]	Ferric citrate coordination complex (N=281)
Serum ferritin, ng/mL	**Baseline**		
	Mean (SD)	609.50 (307.69)	592.80 (292.86)
	Week 52, change from baseline		
	LS mean (SE)	26.13 (34.28)	300.04 (25.22)
	LS difference to placebo (SE)	-	273.92 (42.57)
	95% CI for difference	-	190.22, 357.61
	p-value	-	< 0.0001 [b]
Serum TSAT, %	**Baseline**		
	Mean (SD)	30.8 (11.57)	31.3 (11.21)
	Week 52, change from baseline		
	LS mean (SE)	-1.25 (1.27)	8.07 (0.94)
	LS difference to placebo (SE)	-	9.33 (1.58)
	95% CI for difference	-	6.22, 12.44
	p-value	-	< 0.0001 [b]
Intravenous iron administration, mg/day	Median daily intake over 52 weeks	3.83	1.87
	p-value	-	< 0.0001 [c]
Intravenous ESA administration, units/day	Median daily intake over 52 weeks	993.46	755.80
	p-value	-	0.0473 [c]

A sequential hierarchal testing strategy was used for the primary and secondary efficacy endpoints.
CI=confidence interval; SD=standard deviation; SE=standard error; TSAT=transferrin saturation; ESA=erythropoietin stimulating agent
[a] includes calcium acetate, sevelamer carbonate, or a combination of these; [b] ANCOVA model with treatment as the fixed effect and study baseline as the covariate; [c] 2-sided Wilcoxon Rank Sum Test.

In a post-hoc analysis, there was a decrease in serum haemoglobin over 52 weeks in both treatment arms (see table below), which was less in the ferric citrate coordination complex arm.

Table 5: Summary of haemoglobin results in Study 3

Parameter		Active control (N=146) [a]	Ferric citrate coordination complex (N=281)
Serum haemoglobin, g/dL [b]	**Baseline**		
	Mean (SD)	11.71 (1.26)	11.61 (1.24)
	Week 52, change from baseline		
	LS mean (SE)	-0.52 (0.11)	-0.22 (0.08)
	LS difference to placebo (SE)	-	0.30 (0.14).
	95% CI for difference	-	0.02, 0.57
	p-value	-	0.034 [c]

CI=confidence interval; SD=standard deviation; SE=standard error
[a] includes calcium acetate, sevelamer carbonate, or a combination of these; [b] values can be estimated to mmol/L using conversion factor of 0.6206; [c] ANCOVA model with treatment as fixed effect and study baseline value as the covariate

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ferric citrate coordination complex in one or more subsets of the paediatric population in the treatment

of iron deficiency anaemia in chronic kidney disease (CKD) with elevated serum phosphorus levels (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Formal pharmacokinetic studies have not been performed.
Following oral administration, soluble ferric iron is reduced from the ferric to the ferrous form by ferric reductase in the gastrointestinal (GI) tract. After transport through the enterocytes into the blood, oxidised ferric iron circulates bound to the plasma protein transferrin. It is distributed mainly to the liver, spleen, bone narrow and utilised by incorporation into red blood cells.

Unabsorbed iron from ferric citrate coordination complex interacts with phosphate in the GI tract to form a ferric citrate phosphate complex, an insoluble complex excreted in stool.

Following absorption, citrate is converted into bicarbonate by the tissues.

5.3 Preclinical safety data

The target organ for primary toxicity of ferric citrate coordination complex in repeat-dose oral toxicity studies in rats and dogs is the gastrointestinal tract. Brown pigmentation reflecting iron overload and leading to liver injury was observed in ferric citrate-treated dogs, the most sensitive species, in a 42-week study. The safety margin at the no-observed-adverse-effect level (NOAEL) for the proposed maximal human therapeutic dose of 200 mg/kg (12 g/day) corresponds to 1.1 based on a body surface area.

Ferric citrate coordination complex was neither mutagenic in the bacterial reverse mutation assay (Ames test) nor clastogenic in the chromosomal aberration test in Chinese hamster fibroblasts.

Data from carcinogenicity studies have shown that iron compounds and citric acid are not carcinogenic in mice and rats when administered intramuscularly or subcutaneously.

The potential for ferric citrate coordination complex to impair reproductive performance or to cause foetal malformation has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Pregelatinised starch
Calcium stearate

Film-coating

Hypromellose
Titanium dioxide (E171)
Triacetin
Sunset yellow FCF (E110)
Allura red AC (E129)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Shelf-life after first opening of the bottle: 2 months.

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles sealed with child-resistant polypropylene screw caps, an aluminium foil heat-sealed with a polyethylene liner and two silica gel sachets.
Each bottle contains 200 film-coated tablets and is packed into a carton box.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AVEROA SAS
11 Avenue Paul Verlaine
38100 Grenoble
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1923/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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 responsible for batch release

Patheon France
40 Boulevard de Champaret
38300 Bourgoin Jallieu
France

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 (PSURs)**

The requirements for submission of PSURs 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 (MAH) shall submit the first PSUR 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xoanacyl 1 g film-coated tablets
ferric citrate (as coordination complex)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 g of ferric citrate (as coordination complex, containing 210 mg of ferric iron).

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF (E110) and allura red AC (E129). See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

The tablets must be swallowed whole. Do not chew or crush.

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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °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

AVEROA SAS
11 Avenue Paul Verlaine
38100 Grenoble
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1923/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xoanacyl

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Xoanacyl 1 g film-coated tablets
Ferric citrate (as coordination complex)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 g of ferric citrate (as coordination complex, containing 210 mg of ferric iron).

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF (E110) and allura red AC (E129). See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
The tablets must be swallowed whole. Do not chew or crush.

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: 2 months
Open date: __/___/___

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °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

AVEROA SAS
11 Avenue Paul Verlaine
38100 Grenoble
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1923/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xoanacyl 1 g film-coated tablets
ferric citrate (as coordination complex)

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 Xoanacyl is and what it is used for

Xoanacyl is a medicine that works by binding phosphorus and that contains iron. It is used in adults with impaired kidney function who have high blood phosphorus levels and a lack of iron.

Patients with chronic impaired kidney function are not able to remove phosphorus from their body adequately. This can lead to high phosphorus levels in the blood, which can cause calcium to build-up in tissues (calcification) causing issues such as red eyes, itchy skin and bone pain.
Phosphorus is present in many foods. Xoanacyl attaches to the phosphorus from food in the digestive tract (stomach and bowels) to prevent it from being absorbed into the blood. Phosphorus that is attached to Xoanacyl is then excreted from the body in the stool.

Patients with chronic impaired kidney function can have lower levels of iron. Low iron can cause anaemia (low levels of red blood cells). Xoanacyl provides iron to the body.

2. What you need to know before you take Xoanacyl

Treatment should be initiated under the supervision of your doctor.

Do not take Xoanacyl
- if you are allergic to ferric citrate (as coordination complex) or any of the other ingredients of this medicine (listed in section 6);
- if you have a severe stomach or bowel disease;
- if you have haemochromatosis, a condition causing the body to absorb too much iron from the food you eat, or any other disorder associated with absorbing high levels of iron.

Warnings and precautions
Talk to your doctor or pharmacist before taking Xoanacyl if you have:
- bowel inflammation or bleeding of the stomach (see section 2 “Do not take Xoanacyl”);

- on-going severe stomach and bowel disease (see section 2 “Do not take Xoanacyl”).

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

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

The following medicines should not be taken during treatment with Xoanacyl
- medicines containing aluminium and used to reduce the acidity in your stomach: antacids such as aluminium hydroxide;
- other iron containing medicines and taken by mouth.
-

Your doctor may advise you to take these medicines at least 2 hours before or after Xoanacyl
- a medicine to treat hypothyroidism (lack of thyroid hormone): levothyroxine. The levothyroxine dose may need to be adjusted during treatment with Xoanacyl;
- antibiotic medicines to treat bacterial infections: ciprofloxacin, levofloxacin, doxycycline, cefdinir;
- medicines to treat Parkinson’s disease: levodopa, benserazide, entacapone;
- medicines to treat high blood pressure: captopril, methyldopa;
- a medicine that is used to treat rheumatoid arthritis, Wilson’s disease, cystinuria, lead poisoning: penicillamine;
- medicines used to treat bone loss and help rebuild bone: alendronate sodium, calcium;
- medicines containing calcium and magnesium and used to reduce the acidity in your stomach: antacids such as oxides, hydroxides or salts of magnesium and calcium.

Pregnancy, 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
It is unknown whether Xoanacyl has any effect on unborn babies. Xoanacyl is not recommended during pregnancy and in women who are able to become pregnant not using birth control. 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.

Breast-feeding
It is unknown whether Xoanacyl passes into breast milk. Tell your doctor if you wish to breast-feed your baby when using this medicine. Your doctor will help you decide whether to discontinue breast-feeding or to abstain from Xoanacyl therapy.

Driving and using machines
Xoanacyl has no or negligible influence on your ability to drive and use machines.

Xoanacyl contains sunset yellow FCF (E110) and allura red AC (E129)
These excipients may cause allergic reactions.

3. How to take Xoanacyl

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

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 Xoanacyl.

The maximum dose is 12 film-coated tablets per day.

The recommended starting dose is:
- If you are not on dialysis: 1 film-coated tablet three times per day, with or immediately after main meals of the day;
- If you are on dialysis and you were not already receiving a medicine that lowers your levels of phosphorus: 1 or 2 film-coated tablets three times per day, with or immediately after main meals of the day;
- If you are on dialysis and you were already taking a medicine that lowers your levels of phosphorus: 2 film-coated tablets three times per day, with or immediately after main meals of the day.

Your doctor may decrease or increase the starting dose depending on your blood iron and phosphorus levels. Your doctor will monitor your iron blood tests and phosphorus levels regularly. These blood tests may be part of your routine tests for your kidney disease.

If you have a severe hepatic disease, the recommended starting dose is 1 film-coated tablet three times per day.

Method of use
Swallow the film-coated tablets whole with one glass of water. Do not chew or crush the film-coated tablets because iron can cause discoloration of mouth and teeth.
Your doctor will tell you how many film-coated tablets you should take at each meal.

If you take more Xoanacyl than you should
If you have accidentally taken too many film-coated tablets of Xoanacyl, contact a doctor or poison control centre immediately.
You may feel sick or have diarrhoea, abdominal pain, headache, feel irritated or sleepy. A doctor may need to give you treatment to remove excess iron from your body.
You can have too low levels of phosphorus in your blood. A doctor may temporarily discontinue your treatment.

If you forget to take Xoanacyl
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 Xoanacyl
It is important that you continue taking Xoanacyl 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.

The following side effects have been reported:

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

Common side effects (may affect up to 1 in 10 people):
- belly (abdominal) pain, discomfort and/or swelling

- nausea
- constipation
- indigestion (dyspepsia)
- flatulence

Uncommon side effects (may affect up to 1 in 100 people):
- low phosphorus levels seen in blood test results
- blood in the stool
- haemorrhoids

Not known (frequency cannot be estimated from the available data):
- high iron levels seen in blood test results.

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 Xoanacyl

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 30 °C.
Keep the bottle tightly closed in order to protect from moisture.
After first opening of the bottle, use within 2 months.

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 Xoanacyl contains
- The active substance is ferric citrate (as coordination complex). Each film-coated tablet contains 1 g of ferric citrate (as coordination complex, containing 210 mg of ferric iron).
- The other ingredients are pregelatinised starch and calcium stearate in the core tablet and hypromellose, titanium dioxide (E171), triacetin, sunset yellow FCF (E110), allura red AC (E129) and indigo carmine (E132) in the film-coating (see section 2 "Xoanacyl contains sunset yellow FCF and allura red AC").

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

The film-coated tablets are packed in high density polyethylene (HDPE) bottles sealed with child-resistant polypropylene caps, an aluminium foil sealed with a polyethylene liner and two silica gel sachets included to protect the product from moisture.
Each carton contains one bottle of 200 film-coated tablets.

Marketing Authorisation Holder
AVEROA SAS

11 Avenue Paul Verlaine
38100 Grenoble
France

Manufacturer
Patheon France
40 Boulevard de Champaret
38300 Bourgoin Jallieu
France

This leaflet was last revised in.

Other sources of information

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