1. NAME OF THE MEDICINAL PRODUCT

NEPHOXIL® Capsule 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg ferric citrate (equivalent to 105 mg ferric iron).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule.
Dark red capsule in size #00 and the capsule body is marked with "NE26".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nephoxil is indicated for the control of hyperphosphatemia in adult patients with chronic kidney disease undergoing hemodialysis.

4.2 Posology and method of administration

Posology
The recommended dose of Nephoxil is ranged from 1.5 to 6 g/day. The drug should be taken three times daily with meals or immediately after meals. During the treatment, the dose should be adjusted based on the concentration of serum phosphorus, 1 g (2 capsules) daily per increment or decrement, until serum phosphorus concentration reaches the target range; and afterwards regular monitoring should be maintained and dose adjustments should be made at intervals of one week or more.

Paediatric population
The safety info of Nephoxil has not been established for patients less than 18 years of age.

Elderly population
No significant difference was found between the elderly and younger patients in clinical trials conducted thus far. In general, as the physical condition of the elderly is rather deteriorated, caution should be taken when prescribing the drug.

Method of administration
Oral use. Take Nephoxil capsules intactly with meals or immediately after meals and avoid opening or grounding.

4.3 Contraindications

. Hypophosphatemia
. Hypersensitivity to the active substance.
. Patients with abnormal iron metabolism or symptoms of excessive iron, e.g. hemochromatosis

4.4 Special warnings and precautions for use

Nephoxil should not be co-administration with products containing aluminum. Nephoxil contains citric acid and enhanced absorption of aluminum has been reported when co-administration of citric acid with aluminum containing preparation.

Nephoxil is a calcium-free phosphate binder and therefore serum calcium concentration should be monitored regularly in patients with end-stage kidney disease for hypocalcemia.

Please monitor hematology and biochemistry parameters in monthly basis, at least including albumin, calcium, phosphorus, iron, total iron binding energy (TIBC), serum ferritin, liver index (GOT/GPT), as reference for dosage adjustment.

Like other oral iron preparations, Nephoxil often results in feces discoloration (dark) which is a normal effect for oral iron preparations.

In previous trials, serum ferritin and transferrin saturation may gradually increase with the use of Nephoxil. Therefore, assess iron parameters (such as serum ferritin and TSAT) prior using this drug and monitor iron parameters regularly in the follow-up treatment. When providing medical care for anemia, the dose of IV iron or other oral iron preparations may be adjusted according to the level of serum iron parameters. In previous trials, patients on Nephoxil may require a reduction in dose or discontinuation of IV iron therapy. In addition, do not measure serum iron parameters within two to seven days following administration of IV iron preparations because serum ferritin and TSAT levels will rise rapidly. Do not administer Nephoxil to patients with iron overload.

Caution should be taken to assess patients' overall condition if prescribing Nephoxil to patients with ferritin >800 ng/ml or TSAT >50%. Discontinue using of iron therapy if the symptom of iron overload is observed.

Patients with inflammatory bowel disease, or active, symptomatic gastrointestinal bleeding were excluded from clinical trials and safety has not been established in these populations. One case of gastrointestinal bleeding was reported in a patient administered Nephoxil in postmarketing surveillance. This drug should be carefully used in patients with active and severe gastrointestinal discomfort, such as gastrointestinal bleeding.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1. Drug interactions with Nephoxil

Oral drugs that can be administered concomitantly with Nephoxil:	
Amlodipine Aspirin Atorvastatin Calcitriol Clopidogrel Digoxin Diltiazem Doxercalciferol Enalapril Fluvastatin Glimepiride Levofloxacin Losartan	Metoprolol Pravastatin Propranolol Sitagliptin Warfarin
Oral drugs that have to be separated from Nephoxil and meals:	
	Dosing Recommendations
Doxycycline	Take at least 1 hour before Nephoxil

Ciprofloxacin	Take at least 2 hours before or after Nephoxil

For oral medications not listed in Table 1, there are no empirical data on avoiding drug interactions between Nephoxil and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety information of ferric citrate has not been established for pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3). Ferric citrate should only be given when therapeutic benefits outweigh the risk for pregnant women.

Lactation
There are no human data regarding the effect of ferric citrate in human milk, the effects on the breastfed child, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ferric citrate and any potential adverse effects on the breastfed child from ferric citrate or from the underlying maternal condition.

Fertility
No data are available on the potential influence of ferric citrate on fertility.

4.7 Effects on ability to drive and use machines

Nephoxil has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Important Side Effects/ Adverse Reactions of Clinical Trial
Adverse reactions reported in 2 studies in Nephoxil and a pooled data set of 4 studies in ferric citrate (Total N=901) are listed in following table. The frequency rate was classified as: Very common (≥1/10); Common (≥1/100 to < 1/10); and Uncommon (≥ 1/1,000 to < 1/100).

System Organ Class **Observed Incidence**	**Preferred Term**
Infections and Infestations	
Uncommon	Bronchitis, upper respiratory infection
Metabolism and Nutrition Disorders	
Uncommon	Decreased appetite, hyperkalemia, hypophosphatemia, increased appetite hyperphosphatemia, iron overload, hyperuricaemia
Nervous System Disorders	
Uncommon	Dizziness, headache
Cardiac Disorders	
Uncommon	Palpitations, dyspnoea
Vascular Disorders	
Uncommon	Malignant hypertension, hypertension

Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Pulmonary oedema, wheezing
Gastrointestinal Disorders	
Very common	Discoloured faeces, diarrhoea
Common	Constipation, abdominal pain/discomfort/distension, nauseam, vomiting
Uncommon	Abdominal pain upper, abnormal faeces, anal incontinence, bowel movement irregularity, dry mouth, dysgeusia, dyspepsia, dysphagia, flatulence, frequent bowel movements, gastritis, gastritis erosive, gastroesophageal reflux disease, gastrointestinal haemorrhage, hematemesis, haematochezia, haemorrhoids, melaena, peptic ulcer, soft faeces,
Skin and Subcutaneous Tissue Disorders	
Uncommon	Dermatitis allergic, pruritus, rash, skin discoloration
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle spasms, pain in extremity
Renal and Urinary Disorders	
Uncommon	Incontinence
General Disorders and Administration site Conditions	
Uncommon	Chest pain, inflammation, pain, pyrexia, thirst,
Investigations	
Uncommon	Abnormal breath sounds, decreased haemoglobin, increased serum ferritin, increased transferrin saturation, increased weight,
Injury, Poisoning and Procedural Complications	
Uncommon	Muscle injury, procedural

Based on the clinical experiences, the adverse reactions of Nephoxil are mostly associated to mild to moderate GI tract discomfort, The most common adverse reactions including discolored feces, and diarrhoea, followed by constipation, abdominal pain/ discomfort/ distension, nausea and vomiting.

Ferric citrate is associated with discolored feces (dark stool). This is caused by iron and thus is not clinically relevant. The discoloration does not affect fecal occult blood test which detects heme iron rather than non-heme iron in the stool.

4.9 Overdose

Currently, no overdose of Nephoxil has been reported. In clinical trials, the maximum dose of ferric citrate used for treating patients with chronic kidney disease on hemodialysis is 12 g/day (equivalent to 2,520 mg of ferric iron). Do not administer Nephoxil in patients with iron overload or hemochromatosis.

Iron absorption from ferric citrate may cause excessive iron stores, especially when co-administered with IV iron. In an oversea clinical study, one case of excessive iron in liver as confirmed by biopsy was reported in a patient administered ferric citrate concomitantly with IV iron.

Accidental overdose of iron-containing products in children under six years of age may lead to fatal poisoning. This drug should be stored in a place not accessible to children. In case of accidental overdose, please contact a doctor or medical organization immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The active ingredient of Nephoxil is ferric citrate which can decrease serum phosphorus concentration by reducing the phosphorus absorption in the intestine. The ferric iron of Nephoxil will react with dietary phosphate in the gastrointestinal tract and form an insoluble precipitation of iron phosphate and be eliminated in feces, thereby reducing the concentration of phosphorous in serum. After absorption, the citrate of Nephoxil will be metabolized into bicarbonate.

Pharmacodynamic effects

In addition to lowering serum phosphorus concentration, previous studies indicate ferric citrate can increase the serum iron parameters (ferritin, TSAT and serum iron level). In a 52-week, active-controlled trial, in which IV iron were allowed to be concomitantly administered with ferric citrate (same active ingredient of this product, but in different dosage forms) in hemodialysis patients, the mean (SD) ferritin of the ferric citrate group increased from 593 (293) ng/mL to 895 (482) ng/mL, the mean (SD) TSAT levels increased from 31% (11) to 39% (17), and mean (SD) serum iron level increased from 73 (29) mcg/dL to 88 (42) mcg/dL, whereas relevant parameters in active control group remained relatively constant.

Clinical efficacy

In a 8-week, phase III, placebo-controlled trial, a total of 183 patients with chronic kidney disease undergoing hemodialysis and with hyperphosphatemia (serum phosphorus> 5.5 mg/dL) were randomized to Nephoxil 6 g/day, 4 g/day and the placebo group. A significant reduction of the serum phosphorus level is observed in the first week in the groups of Nephoxil 6 g/day and 4 g/day; at the last observation on day 57, the mean reductions in serum phosphorus level were 2.27 mg/dL with Nephoxil 6 g/day group, and 1.60 mg/dL with Nephoxil 4 g/day group. The results demonstrate that both Nephoxil groups can effectively reduce serum phosphorous when compared to the placebo group ($p<0.001$).

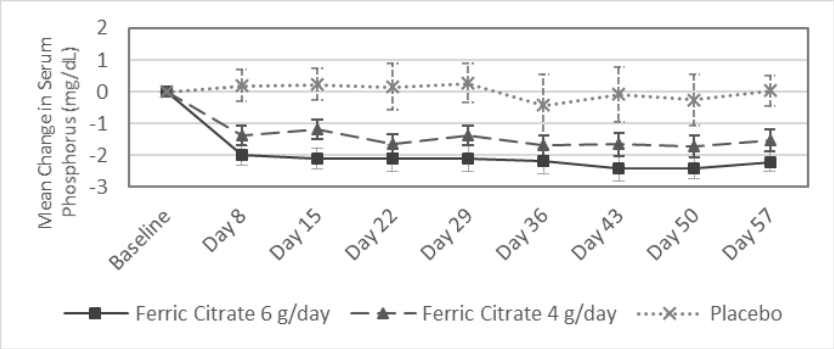
The mean serum ferritin levels at baseline and at the end of treatment (Day 57) were 351.29 ng/ml and 427.57 ng/ml in Nephoxil 6 g/day group, respectively; 354.62 ng/mL and 436.04 ng/ml in Nephoxil 4 g/day group, respectively; and 393.54 ng/ml and 402.43 ng/ml in the placebo group, respectively. The mean TSAT levels at baseline and the end of treatment (Day 57) were 26.75% and 31.90% in Nephoxil 6 g/day group, respectively; 27.22% and 31.74% in Nephoxil 4 g/day group, respectively; and 30.22% and 25.62% in the placebo group, respectively.

Table 2. Changes of the Serum Phosphorous Concentration by Treatment Groups

Average serum phosphorous concentration (mg/dL)	Nephoxil 6 g/day (N=66)*	Nephoxil 4 g/day (N=72)*	Placebo (N=28)
Baseline (after washout)	6.95	6.96	7.37
End of Treatment (Day 57)	4.69	5.38	7.42
Mean change from baseline	-2.27*	-1.60*	0.08
Compared with the placebo group LS mean P value**	 -2.51 <0.001	 -1.83 <0.001	

*Efficacy population consisted of all safety population subjects who had a pre-dose and (at least once) non-missing Study Day 15 or later serum phosphorus level measurement.
**Analysis using ANCOVA

Figure 1. Mean Changes in Serum Phosphorus over 8 Weeks

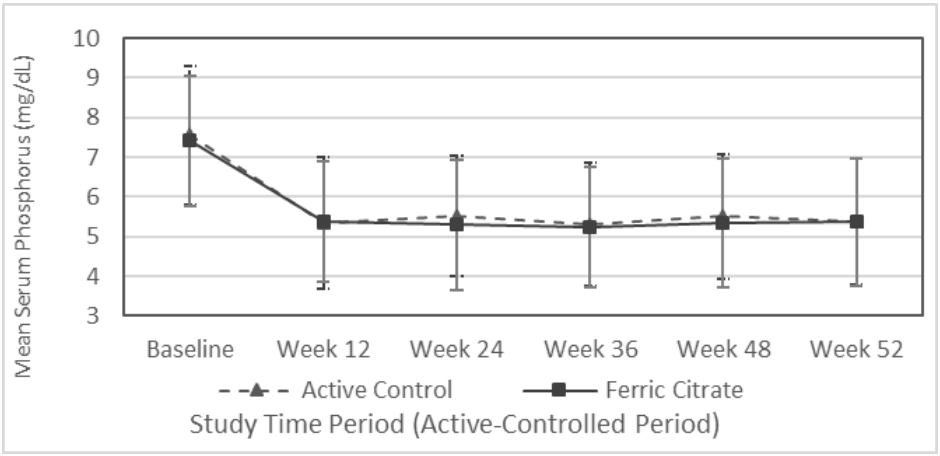


In a long-term, open-labeled observational study, a total of 202 patients with chronic kidney disease undergoing hemodialysis were treated with Nephoxil for 52 weeks. Patients were switched to the treatment of Nephoxil directly without washout from prior oral phosphate binders. The dose of Nephoxil was adjusted based on the serum phosphorus level during the study. The target range of serum phosphorus level was 3.5~5.5mg/dL. There were no strict restriction of concomitant use of other oral phosphorus binders or other treatments that might affect serum phosphorus level during the study. Among the 119 patients who had completed the study, more than 90% of patients received the mean daily dose between 1.5~6 g/day. Results from the full analysis set (FAS) of 197 patients showed that the mean serum phosphorus was 5.38 mg/dL at baseline and 5.10 mg/dL at the end of the study (Week 52); and the achievement rate of target serum phosphorus level (3.5~5.5 mg/dL) was 54.8% at baseline and 59.8% at the end of the study (Week 52).

The following data is obtained from a 56-week oversea trial which was divided into two phases: a 52-week, active-controlled phase and a 4-week, placebo-controlled phase. The drug tested in the trial contains the same active ingredient of this product, but in different dosage forms.

After the 2-week washout period, the hemodialysis patients with a mean serum phosphorus concentration higher than 7.5 mg/dL were randomized into ferric citrate group (N=292) or active-controlled group (calcium acetate, and/or Sevelamer carbonate or both, N=149) in the ratios of 2:1. Most subjects (>96%) were on hemodialysis. The starting dose of the ferric citrate group was 6 grams per day and be taken with meals. The starting dose of the active control was the patient's dose prior to the washout period. The dose of ferric citrate and active drug were titrated according to serum phosphorus level with a target phosphorus level of 3.5-5.5mg/dL, and the maximum daily dose of ferric citrate was 12 grams. The study results indicated that serum phosphorus level reduced following initiation of treatment, and the phosphorus-lowering effect can be maintained until Week 52.

Figure 2. Mean Serum Phosphorous Concentration over 52 Weeks



Following completion of the 52-week active-controlled phase, patients in the ferric citrate group then entered a 4-week placebo-controlled, randomized withdrawal phase, in which patients were randomized in a 1:1 ratio to receive ferric citrate (N=96) or placebo (N=96). During the placebo-controlled phase, serum phosphorus concentration of placebo group showed an increase of 2.2 mg/dL relative to ferric citrate group.

Table 3. Effect of Ferric Citrate on Serum Phosphorous during Placebo-controlled Phase

Mean serum phosphorous (mg/dL)	Ferric citrate group	Placebo group	Treatment difference (95% CI)	p-Value
Mean baseline (Week 52)	5.12	5.44		
Mean change from baseline (Week 56)	-0.24	1.79	-2.18 (-2.59, -1.77)	<0.0001*

* The LS mean treatment difference and p-value for the change in mean were created via an ANCOVA model with treatment as the fixed effect and Week-52 baseline (phosphorus) or Study-baseline (ferritin and TSAT) as the covariate. Between-treatment differences were calculated as LS mean (ferric citrate group) minus LS mean (placebo group)

5.2 Pharmacokinetic properties

No formal pharmacokinetic studies of ferric citrate have been conducted. According to the mechanism of action, most of the ferric iron of ferric citrate is eliminated in feces and is not absorbed. The clinical data has shown that some portion of the unbound iron which does not interacts with phosphate will be absorbed in long-term, and result in increases of serum iron parameters.

5.3 Preclinical safety data

The non-clinical program 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 ferric citrate were derived from the repeat dose toxicology studies, and did not reveal safety concerns for humans.

Data from carcinogenesis 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin capsule (Gelatin, Titanium Dioxide, Tartrazine, Sodium Lauryl Sulfate, Brilliant Blue FCF, Allura Red AC, Purified Water).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years when stored at and below 30 °C in the HDPE bottle

6.4 Special precautions for storage

Store at or below 30°C and protected from humidity and light.

6.5 Nature and contents of container

Nephoxil capsules are packaged with desiccant in a HDPE bottle. The bottle is capped and heat sealed with aluminum foil.

Pack size per bottle:
90 capsules

6.6 Special precautions for disposal

No special requirement for disposal. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

DKSH (Thailand) Limited
Bangkok, Thailand

Manufacturer
Panion & BF Biotech Inc, Pingjhen Plant (Taiwan) No. 266, Xinglong Rd., Pingjhen Dist., Taoyuan City, Taiwan (R.O.C.)

8. MARKET AUTHORIZATION NUMBER

1C 15072/66 (NC)

9. DATE OF AUTHORIZATION

22 September 2023

10. DATE OF REVISION OF THE TEXT

22 September 2023