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

BindRen 1 g film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 g colestilan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, oval shaped, film-coated tablet approximately 20.2 mm in length and 10.7 mm wide printed with "BINDREN" (in blue ink) on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BindRen is indicated for the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis.

4.2 Posology and method of administration

Posology
The recommended starting dose is 6-9 g per day (2-3 g three times daily).

Patients previously on other phosphate binders who are switched to BindRen should start taking 6-9 g per day (2-3 g three times daily).

Dose titration
Serum phosphorus concentrations should be monitored. If an acceptable serum phosphorus concentration is not achieved, the dose may be increased by 3 g per day (1 g three times daily) in 2-3 weekly intervals. The maximum daily dose of BindRen tested in clinical trials was 15 g per day (5 g three times daily).

Special populations
Elderly population
Experience from clinical studies in patients above the age of 75 years is very limited.

Renal impairment
BindRen is indicated for use in patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis. No data on the use of BindRen in pre-dialysis patients are available.

Severe hepatic impairment
Patients with severe hepatic impairment were excluded from clinical studies. Therefore, the use of BindRen is not recommended in patients with severe hepatic impairment (see also section 4.4). No data are available.

Paediatric population
The safety and efficacy of BindRen in children and adolescents aged under 18 years has not yet been established. No data are available.

Method of administration
BindRen is for oral use. Tablets should be taken whole.
The daily dose of BindRen tablets should be taken in three equally divided doses with or immediately after meals with a sufficient amount of water to aid swallowing.
The division of the daily dose may be adjusted on a physician's advice taking into account the dietary intake of phosphate. Patients should be encouraged to adhere to their prescribed low phosphate diets.
Treatment of high blood phosphorus levels usually requires long-term treatment.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Bowel obstruction.

4.4 Special warnings and precautions for use

The safety and efficacy of BindRen has not been studied in patients with:
- Dysphagia or swallowing disorders
- Severe gastrointestinal disorders such as chronic or severe constipation, intestinal stenosis, intestinal diverticulum, sigmoid colitis, gastrointestinal ulcers, or recent major gastrointestinal surgery
- Biliary obstruction
- Severe hepatic impairment (see also section 4.2)
- Seizure disorders
- Recent history of peritonitis in peritoneal dialysis patients
- Serum albumin <30 g/L

Therefore, the use of BindRen is not recommended in patients with these disorders.

Hyperparathyroidism
BindRen alone is not indicated for the control of hyperparathyroidism.

Intestinal obstruction and ileus/subileus
In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with BindRen. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with BindRen. In patients who develop severe constipation or other severe gastrointestinal symptoms, alternative treatment may need to be considered.

Gastrointestinal haemorrhage
Caution should be exercised when treating patients with conditions which predispose to gastrointestinal haemorrhage, such as recent history of gastrointestinal haemorrhage, gastrointestinal ulcers, gastritis, diverticulosis, colitis and haemorrhoids.

Hypocalcaemia/hypercalcaemia
Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. BindRen does not contain calcium, and has no effect on serum calcium concentrations on treatment for up to one year. Serum calcium concentrations should be monitored as a normal follow-up of a dialysis patient. Elemental calcium should be given as a supplement in case of hypocalcaemia.

Fat-soluble vitamins
BindRen did not induce any clinically relevant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption syndromes and patients treated with coumarin anticoagulants (e.g. warfarin). In these patients, monitoring of vitamin A, D and E concentrations or assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.

Folate deficiency
BindRen did not induce a clinically relevant reduction in folate absorption during clinical studies of up to one year. However, intestinal folate absorption may be impaired during long-term treatment of BindRen. In these patients, monitoring serum folate status and supplementation with folic acid should be considered.

Hypothyroidism
Close monitoring of patients with hypothyroidism is recommended when levothyroxine is co-administered with BindRen (see section 4.5).

Systemic ion balance
BindRen binds phosphate and bile acid, with the release of chloride which is available for systemic absorption. Changes in systemic ion balance with an increase in chloride and decrease in bicarbonate are therefore possible. However, BindRen did not induce any clinically relevant change in chloride and bicarbonate on treatment for up to one year.

4.5 Interaction with other medicinal products and other forms of interaction

BindRen is not absorbed from the gastrointestinal tract but may affect the bioavailability or absorption rate of other medicinal products. In addition, reduced bioavailability of other medicinal products by changes in enterohepatic circulation, for example, steroid hormones with potential impairment of the effectiveness of oral contraceptives, have been reported for medicinal products with a similar mechanism of action to BindRen. When administering any medicinal product where a reduction in the bioavailability could have a clinically relevant effect on safety or efficacy, the medicinal product should be administered at least 1 hour before, or 3 hours after taking BindRen. Concomitant treatment with medicinal products with a narrow therapeutic window requires close monitoring of drug concentrations or adverse reactions, on initiation or dose-adjustment of either BindRen or the concomitant medicinal product.

Interaction studies have been conducted in healthy volunteers. Interactions have not been studied at doses >9 g daily, and greater interaction effects at higher doses of BindRen cannot be excluded.

Single dose interaction studies demonstrated that the bioavailability of ciprofloxacin, warfarin and enalapril were not affected when co-administered with BindRen (6-9 g/day). BindRen lowered the bioavailability of digoxin by 16% and C_{max} by 17%, and the C_{max} of enalapril by 27%.

Due to the high *in vitro* binding potential between BindRen and levothyroxine, closer monitoring of thyroid stimulating hormone (TSH) levels in patients receiving BindRen and levothyroxine is recommended.

No *in vivo* data are available on the possible interaction of BindRen on the absorption of the immunosuppressant medicinal products mycophenolate mofetil, ciclosporin or tacrolimus. However, decreased blood concentrations have been reported for medicinal products with a similar mechanism of action to BindRen. Caution should be exercised when prescribing BindRen to patients receiving immunosuppressants.

Patients with seizure disorders were excluded from clinical trials with BindRen. Caution should be exercised when prescribing BindRen to patients also taking anti-seizure medicinal products.

4.6 Fertility, pregnancy and lactation

BindRen is not absorbed and is not systemically available. No direct effects of BindRen are thus anticipated. However, other effects of BindRen may affect pregnant and breast-feeding women or influence fertility, see sections 4.4 and 4.5.

Pregnancy
No data are available to assess the safety and efficacy in pregnant women.
Patients that become pregnant and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.

Breast-feeding
No data are available to assess the safety and efficacy in breast-feeding women.
Patients that breast-feed and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.

Fertility
No data are available to assess the potential influence of BindRen on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The Phase II and III clinical studies involving 1,410 patients with CKD Stage 5 on dialysis treated with BindRen for up to one year constituted the safety population. Patients received doses of up to 15 g per day, in three divided doses of 5 g.

Approximately 30% of patients experienced at least one adverse reaction. The most serious adverse reactions were gastrointestinal haemorrhage (uncommon) and constipation (common). The most frequently reported adverse reactions were nausea, dyspepsia and vomiting (all common). The frequency of adverse reactions increased with dose.

Tabulated list of adverse reactions
A tabulated list of frequencies was 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations	
Uncommon:	Gastroenteritis
Endocrine disorders	
Uncommon:	Hyperparathyroidism
Metabolism and nutrition disorders	
Common:	Hypocalcaemia, decreased appetite
Uncommon:	Folate deficiency, hypertriglyceridaemia, polydipsia
Rare:	Vitamin K deficiency, calciphylaxis, electrolyte imbalance, fluid overload
Psychiatric disorders	
Uncommon:	Insomnia
Nervous system disorders	
Uncommon:	Tremor, dizziness, headache, dysgeusia
Cardiac disorders	
Rare:	Coronary artery disease
Vascular disorders	
Uncommon:	Haematoma, hypotension

Gastrointestinal disorders	
Common:	Constipation, abdominal pain, vomiting, abdominal distension, nausea, gastritis, dyspepsia, diarrhoea, flatulence, abdominal discomfort
Uncommon:	Gastrointestinal haemorrhage, oesophagitis, faecaloma, dysphagia, change in bowel habit, dry mouth
Rare:	Intestinal obstruction*
Hepatobiliary disorders	
Uncommon:	Hepatic enzymes increased
Skin and subcutaneous tissue disorders	
Uncommon:	Urticaria, rash, pruritus, dry skin
Rare:	Allergic dermatitis, guttae psoriasis
Musculoskeletal and connective tissue disorders	
Uncommon:	Muscle spasm, musculoskeletal pain, arthralgia, back pain, pain in extremities
General disorders and administration site conditions	
Uncommon:	Asthenia

*A single case with a fatal outcome

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

BindRen has been given to dialysis patients in doses up to 15 g/day for up to one year continuously with no cases of overdose. The potential risk of overdosing could include adverse reactions or a worsening of adverse reactions mentioned in section 4.8.

There are no known antidotes to BindRen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned

BindRen contains colestilan. Colestilan is a non-absorbed, non-calcium, non-metallic phosphate-binding polymer. The binding sites become partially protonated in the stomach and interact through ionic and hydrogen bonding with both dietary phosphate anions and bile acids in the duodenum. By binding phosphate from food in the digestive tract, colestilan lowers the serum phosphorus concentration. Colestilan also binds bile acids, thereby lowering the serum LDL-cholesterol concentration. Changes in the bile acid pool in the gastrointestinal tract have also been observed to lower serum glucose. Colestilan may also bind uric acid in the gastrointestinal tract.

Three Phase III studies and two long term follow-up studies have been performed in patients with CKD Stage 5 on dialysis, in order to investigate efficacy and safety in this population.

Serum phosphorus
Fixed-dose study:
In a double-blind, 12-week fixed-dose study with five colestilan groups (3, 6, 9, 12 and 15 g/day) and placebo, colestilan at 6 g/day and above demonstrated a dose-dependent reduction in serum phosphorus level. The least squares mean reduction from baseline to week 12 as compared to placebo was 0.16, 0.21, 0.19 and 0.37 mmol/L at 6, 9, 12 and 15 g/day respectively.

Flexible-dose studies:
Two similar 12-week, open-label, flexible-dose studies followed by a 4-week double-blind withdrawal period (comparison to placebo) were performed. In the first study, the mean serum phosphorus level was 2.33 mmol/L at baseline and 1.96 mmol/L (mean reduction by 0.36 mmol/L) at week 12 on a colestilan mean daily dose of 11.5 g. Similarly in the second study, the mean serum phosphorus level was 2.44 mmol/L at baseline and 1.94 mmol/L at week 12 (mean reduction by 0.50 mmol/L) on a colestilan mean daily dose of 13.1 g. The rate of responders (either a reduction in serum phosphorus $\leq$ 1.78 mmol/L and/or a reduction from baseline $\geq$ 0.3 mmol/L) was 50.4 % and 43.8% in the two studies, respectively (placebo 30.8% and 26.3%, respectively).

Long-term studies:
Two long-term, open-label, flexible-dose studies demonstrated that serum phosphorus reduction was maintained for up to one year. After one year, the mean serum phosphorus level was 1.89 mmol/L with a significant reduction from baseline of 0.39 mmol/L and responder rate (phosphorus level <1.78 mmol/L) was 44%. A majority of patients received 12 or 15 g/day of colestilan in the long-term studies.

Serum calcium
In clinical studies, colestilan had no effect on serum calcium levels over a period of up to one year.

Serum calcium-phosphorus ion product
Calcium-phosphorus ion product was reduced by at least 0.48 $mmol^2/L^2$ at week 12 compared to placebo at doses $\geq$9 g/day in fixed-dose study and by 1.05 and 0.86 $mmol^2/L^2$ at week 12 in two flexible-dose studies. Colestilan reduced calcium-phosphorus ion product by 0.90 $mmol^2/L^2$ after one year.

Serum parathyroid hormone (PTH)
In most clinical studies, colestilan decreased serum PTH compared to baseline, and was statistically significant against placebo.

Serum cholesterol
Colestilan significantly reduced serum LDL-cholesterol by 17.8, 25.6, 29.4, 34.8 and 33.4% at 3, 6, 9, 12 and 15 g/day at week 12 compared to placebo in fixed-dose study, respectively. Colestilan also showed significant reductions from baseline by 35.3 and 30.1% at week 12 in two flexible-dose studies, and by 25.8% after one year in long-term studies. The reductions in LDL-cholesterol are also reflected in significant falls in total cholesterol.

Serum glycosylated haemoglobin A1c
In subjects with baseline HbA1c $\geq$7.0%, colestilan showed a reduction of between 0.36 to 1.38% at week 12 in the fixed-dose study, and by 0.94 and 0.91% at week 12 in the two flexible-dose studies. After one year of treatment, a reduction of 1.12% in HbA1c was observed.

Serum uric acid
Colestilan was also associated in dose-dependent reduction in serum uric acid, with a mean reduction of 43 micromol/L after one year of treatment.

5.2 Pharmacokinetic properties

BindRen is not absorbed from the gastrointestinal tract of healthy volunteers following oral administration of ^{14}C-radiolabelled colestilan.

The results of *in vitro* testing suggest that medicinal products with anionic and/or lipophilic characteristics have a higher potential to bind to BindRen.

5.3 Preclinical safety data

Non-clinical data reveal no direct special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development. However, reproductive toxicity studies were not conducted at doses higher than 2.5 times the human clinical dose, and the possible reproductive effects related to coagulation and bleeding have not been assessed.

Haemorrhage and increased clotting parameters (PT and aPTT) were evident in rats following repeat administration. These were considered to result from a deficiency of vitamin K following a reduction in the absorption of fat-soluble vitamins (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Purified water
Hydroxypropylcellulose
Silica, colloidal anhydrous
Castor oil, hydrogenated

Film-coating
Hypromellose
Acetic acid esters of mono- and diglycerides of fatty acids
Polysorbate 80

Printing ink
Shellac
Indigo carmine aluminium lake (E 132)
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles, with a polypropylene cap and an induction seal.

Aluminium/polychlorotrifluoroethylene/PVC blister.

Pack sizes of 45, 99, 198, 270 or 297 tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Mitsubishi Pharma Europe Ltd.
Dashwood House
69 Old Broad Street
London
EC2M 1QS
United Kingdom

Tel: +44 (0)207 065 5000
Fax: +44 (0)207 065 5050
Email: information@mitsubishi-pharma.eu

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/001-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

10. DATE OF REVISION OF THE TEXT

8 August 2013

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

▼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

BindRen 2 g granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 2 g colestilan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules.
White, cylindrical, film-coated granules, each approximately 3.5 mm in length and 3 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BindRen is indicated for the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis.

4.2 Posology and method of administration

Posology
The recommended starting dose is 6-9 g per day (2-3 g three times daily).

Patients previously on other phosphate binders who are switched to BindRen should start taking 6-9 g per day (2-3 g three times daily).

Dose titration
Serum phosphorus concentrations should be monitored. If an acceptable serum phosphorus concentration is not achieved, the dose may be increased by 3 g per day (1 g three times daily) in 2-3 weekly intervals. The maximum daily dose of BindRen tested in clinical trials was 15 g per day (5 g three times daily).

Special populations
Elderly population
Experience from clinical studies in patients above the age of 75 years is very limited.

Renal impairment
BindRen is indicated for use in patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis. No data on the use of BindRen in pre-dialysis patients are available.

Severe hepatic impairment
Patients with severe hepatic impairment were excluded from clinical studies. Therefore, the use of BindRen is not recommended in patients with severe hepatic impairment (see also section 4.4). No data are available.

Paediatric population

The safety and efficacy of BindRen in children and adolescents aged under 18 years has not yet been established. No data are available.

Method of administration
BindRen is for oral use. Granules should be taken whole as one dose from the sachet.
The daily dose of BindRen granules should be taken in three equally divided doses with or immediately after meals with a sufficient amount of water to aid swallowing.
The division of the daily dose may be adjusted on a physician's advice taking into account the dietary intake of phosphate. Patients should be encouraged to adhere to their prescribed low phosphate diets.
Treatment of high blood phosphorus levels usually requires long-term treatment.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Bowel obstruction.

4.4 Special warnings and precautions for use

The safety and efficacy of BindRen has not been studied in patients with:
- Dysphagia or swallowing disorders
- Severe gastrointestinal disorders such as chronic or severe constipation, intestinal stenosis, intestinal diverticulum, sigmoid colitis, gastrointestinal ulcers, or recent major gastrointestinal surgery
- Biliary obstruction
- Severe hepatic impairment (see also section 4.2)
- Seizure disorders
- Recent history of peritonitis in peritoneal dialysis patients
- Serum albumin <30 g/L

Therefore, the use of BindRen is not recommended in patients with these disorders.

Hyperparathyroidism
BindRen alone is not indicated for the control of hyperparathyroidism.

Intestinal obstruction and ileus/subileus
In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with BindRen. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with BindRen. In patients who develop severe constipation or other severe gastrointestinal symptoms, alternative treatment may need to be considered.

Gastrointestinal haemorrhage
Caution should be exercised when treating patients with conditions which predispose to gastrointestinal haemorrhage, such as recent history of gastrointestinal haemorrhage, gastrointestinal ulcers, gastritis, diverticulosis, colitis and haemorrhoids.

Hypocalcaemia/hypercalcaemia
Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. BindRen does not contain calcium, and has no effect on serum calcium concentrations on treatment for up to one year. Serum calcium concentrations should be monitored as a normal follow-up of a dialysis patient. Elemental calcium should be given as a supplement in case of hypocalcaemia.

Fat-soluble vitamins
BindRen did not induce any clinically relevant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption syndromes and patients treated with coumarin anticoagulants (e.g. warfarin). In these patients, monitoring of vitamin A, D and E concentrations or assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.

Folate deficiency
BindRen did not induce a clinically relevant reduction in folate absorption during clinical studies of up to one year. However, intestinal folate absorption may be impaired during long-term treatment of BindRen. In these patients, monitoring serum folate status and supplementation with folic acid should be considered.

Hypothyroidism
Close monitoring of patients with hypothyroidism is recommended when levothyroxine is co-administered with BindRen (see section 4.5).

Systemic ion balance
BindRen binds phosphate and bile acid, with the release of chloride which is available for systemic absorption. Changes in systemic ion balance with an increase in chloride and decrease in bicarbonate are therefore possible. However, BindRen did not induce any clinically relevant change in chloride and bicarbonate on treatment for up to one year.

4.5 Interaction with other medicinal products and other forms of interaction

BindRen is not absorbed from the gastrointestinal tract but may affect the bioavailability or absorption rate of other medicinal products. In addition, reduced bioavailability of other medicinal products by changes in enterohepatic circulation, for example, steroid hormones with potential impairment of the effectiveness of oral contraceptives, have been reported for medicinal products with a similar mechanism of action to BindRen. When administering any medicinal product where a reduction in the bioavailability could have a clinically relevant effect on safety or efficacy, the medicinal product should be administered at least 1 hour before, or 3 hours after taking BindRen. Concomitant treatment with medicinal products with a narrow therapeutic window requires close monitoring of drug concentrations or adverse reactions, on initiation or dose-adjustment of either BindRen or the concomitant medicinal product.

Interaction studies have been conducted in healthy volunteers. Interactions have not been studied at doses >9 g daily, and greater interaction effects at higher doses of BindRen cannot be excluded.

Single dose interaction studies demonstrated that the bioavailability of ciprofloxacin, warfarin and enalapril were not affected when co-administered with BindRen (6-9 g/day). BindRen lowered the bioavailability of digoxin by 16% and C_{max} by 17%, and the C_{max} of enalapril by 27%.

Due to the high *in vitro* binding potential between BindRen and levothyroxine, closer monitoring of thyroid stimulating hormone (TSH) levels in patients receiving BindRen and levothyroxine is recommended.

No *in vivo* data are available on the possible interaction of BindRen on the absorption of the immunosuppressant medicinal products mycophenolate mofetil, ciclosporin or tacrolimus. However, decreased blood concentrations have been reported for medicinal products with a similar mechanism of action to BindRen. Caution should be exercised when prescribing BindRen to patients receiving immunosuppressants.

Patients with seizure disorders were excluded from clinical trials with BindRen. Caution should be exercised when prescribing BindRen to patients also taking anti-seizure medicinal products.

4.6 Fertility, pregnancy and lactation

BindRen is not absorbed and is not systemically available. No direct effects of BindRen are thus anticipated. However, other effects of BindRen may affect pregnant and breast-feeding women or influence fertility, see sections 4.4 and 4.5.

Pregnancy
No data are available to assess the safety and efficacy in pregnant women.
Patients that become pregnant and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.

Breast-feeding
No data are available to assess the safety and efficacy in breast-feeding women.
Patients that breast-feed and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.

Fertility
No data are available to assess the potential influence of BindRen on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The Phase II and III clinical studies involving 1,410 patients with CKD Stage 5 on dialysis treated with BindRen for up to one year constituted the safety population. Patients received doses of up to 15 g per day, in three divided doses of 5 g.

Approximately 30% of patients experienced at least one adverse reaction. The most serious adverse reactions were gastrointestinal haemorrhage (uncommon) and constipation (common). The most frequently reported adverse reactions were nausea, dyspepsia and vomiting (all common). The frequency of adverse reactions increased with dose.

Tabulated list of adverse reactions
A tabulated list of frequencies was 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations	
Uncommon:	Gastroenteritis
Endocrine disorders	
Uncommon:	Hyperparathyroidism
Metabolism and nutrition disorders	
Common:	Hypocalcaemia, decreased appetite
Uncommon:	Folate deficiency, hypertriglyceridaemia, polydipsia
Rare:	Vitamin K deficiency, calciphylaxis, electrolyte imbalance, fluid overload
Psychiatric disorders	
Uncommon:	Insomnia
Nervous system disorders	
Uncommon:	Tremor, dizziness, headache, dysgeusia
Cardiac disorders	
Rare:	Coronary artery disease
Vascular disorders	
Uncommon:	Haematoma, hypotension

Gastrointestinal disorders	
Common:	Constipation, abdominal pain, vomiting, abdominal distension, nausea, gastritis, dyspepsia, diarrhoea, flatulence, abdominal discomfort
Uncommon:	Gastrointestinal haemorrhage, oesophagitis, faecaloma, dysphagia, change in bowel habit, dry mouth
Rare:	Intestinal obstruction*
Hepatobiliary disorders	
Uncommon:	Hepatic enzymes increased
Skin and subcutaneous tissue disorders	
Uncommon:	Urticaria, rash, pruritus, dry skin
Rare:	Allergic dermatitis, guttae psoriasis
Musculoskeletal and connective tissue disorders	
Uncommon:	Muscle spasm, musculoskeletal pain, arthralgia, back pain, pain in extremities
General disorders and administration site conditions	
Uncommon:	Asthenia

*A single case with a fatal outcome

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

BindRen has been given to dialysis patients in doses up to 15 g/day for up to one year continuously with no cases of overdose. The potential risk of overdosing could include adverse reactions or a worsening of adverse reactions mentioned in section 4.8.

There are no known antidotes to BindRen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned

BindRen contains colestilan. Colestilan is a non-absorbed, non-calcium, non-metallic phosphate-binding polymer. The binding sites become partially protonated in the stomach and interact through ionic and hydrogen bonding with both dietary phosphate anions and bile acids in the duodenum. By binding phosphate from food in the digestive tract, colestilan lowers the serum phosphorus concentration. Colestilan also binds bile acids, thereby lowering the serum LDL-cholesterol concentration. Changes in the bile acid pool in the gastrointestinal tract have also been observed to lower serum glucose. Colestilan may also bind uric acid in the gastrointestinal tract.

Three Phase III studies and two long term follow-up studies have been performed in patients with CKD Stage 5 on dialysis, in order to investigate efficacy and safety in this population.

Serum phosphorus
Fixed-dose study:
In a double-blind, 12-week fixed-dose study with five colestilan groups (3, 6, 9, 12 and 15 g/day) and placebo, colestilan at 6 g/day and above demonstrated a dose-dependent reduction in serum phosphorus level. The least squares mean reduction from baseline to week 12 as compared to placebo was 0.16, 0.21, 0.19 and 0.37 mmol/L at 6, 9, 12 and 15 g/day respectively.

Flexible-dose studies:
Two similar 12-week, open-label, flexible-dose studies followed by a 4-week double-blind withdrawal period (comparison to placebo) were performed. In the first study, the mean serum phosphorus level was 2.33 mmol/L at baseline and 1.96 mmol/L (mean reduction by 0.36 mmol/L) at week 12 on a colestilan mean daily dose of 11.5 g. Similarly in the second study, the mean serum phosphorus level was 2.44 mmol/L at baseline and 1.94 mmol/L at week 12 (mean reduction by 0.50 mmol/L) on a colestilan mean daily dose of 13.1 g. The rate of responders (either a reduction in serum phosphorus $\leq$ 1.78 mmol/L and/or a reduction from baseline $\geq$ 0.3 mmol/L) was 50.4 % and 43.8% in the two studies, respectively (placebo 30.8% and 26.3%, respectively).

Long-term studies:
Two long-term, open-label, flexible-dose studies demonstrated that serum phosphorus reduction was maintained for up to one year. After one year, the mean serum phosphorus level was 1.89 mmol/L with a significant reduction from baseline of 0.39 mmol/L and responder rate (phosphorus level <1.78 mmol/L) was 44%. A majority of patients received 12 or 15 g/day of colestilan in the long-term studies.

Serum calcium
In clinical studies, colestilan had no effect on serum calcium levels over a period of up to one year.

Serum calcium-phosphorus ion product
Calcium-phosphorus ion product was reduced by at least 0.48 $mmol^2/L^2$ at week 12 compared to placebo at doses $\geq$9 g/day in fixed-dose study and by 1.05 and 0.86 $mmol^2/L^2$ at week 12 in two flexible-dose studies. Colestilan reduced calcium-phosphorus ion product by 0.90 $mmol^2/L^2$ after one year.

Serum parathyroid hormone (PTH)
In most clinical studies, colestilan decreased serum PTH compared to baseline, and was statistically significant against placebo.

Serum cholesterol
Colestilan significantly reduced serum LDL-cholesterol by 17.8, 25.6, 29.4, 34.8 and 33.4% at 3, 6, 9, 12 and 15 g/day at week 12 compared to placebo in fixed-dose study, respectively. Colestilan also showed significant reductions from baseline by 35.3 and 30.1% at week 12 in two flexible-dose studies, and by 25.8% after one year in long-term studies. The reductions in LDL-cholesterol are also reflected in significant falls in total cholesterol.

Serum glycosylated haemoglobin A1c
In subjects with baseline HbA1c $\geq$7.0%, colestilan showed a reduction of between 0.36 to 1.38% at week 12 in the fixed-dose study, and by 0.94 and 0.91% at week 12 in the two flexible-dose studies. After one year of treatment, a reduction of 1.12% in HbA1c was observed.

Serum uric acid
Colestilan was also associated in dose-dependent reduction in serum uric acid, with a mean reduction of 43 micromol/L after one year of treatment.

5.2 Pharmacokinetic properties

BindRen is not absorbed from the gastrointestinal tract of healthy volunteers following oral administration of ^{14}C-radiolabelled colestilan.

The results of *in vitro* testing suggest that medicinal products with anionic and/or lipophilic characteristics have a higher potential to bind to BindRen.

5.3 Preclinical safety data

Non-clinical data reveal no direct special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development. However, reproductive toxicity studies were not conducted at doses higher than 2.5 times the human clinical dose, and the possible reproductive effects related to coagulation and bleeding have not been assessed.

Haemorrhage and increased clotting parameters (PT and aPTT) were evident in rats following repeat administration. These were considered to result from a deficiency of vitamin K following a reduction in the absorption of fat-soluble vitamins (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granule core
Purified water
Hydroxypropylcellulose
Silica, colloidal anhydrous
Castor oil, hydrogenated

Film-coating
Ethylcellulose
Hypromellose
Macrogol 8000
Triethyl citrate
Titanium dioxide
Talc
Cetyl alcohol
Sodium laurilsulfate
Castor oil, hydrogenated

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Foil laminate (polyethylene terephthalate/polyethylene/aluminium foil/polyethylene/polyvinylidene chloride) sachets.
Each sachet contains 2 g of granules.

Pack sizes:
30, 60 or 90 sachets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Mitsubishi Pharma Europe Ltd.
Dashwood House
69 Old Broad Street
London
EC2M 1QS
United Kingdom

Tel: +44 (0)207 065 5000
Fax: +44 (0)207 065 5050
Email: information@mitsubishi-pharma.eu

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/011-013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

10. DATE OF REVISION OF THE TEXT

8 August 2013

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

▼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

BindRen 3 g granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 3 g colestilan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules.
White, cylindrical, film-coated granules, each approximately 3.5 mm in length and 3 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BindRen is indicated for the treatment of hyperphosphataemia in adult patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis.

4.2 Posology and method of administration

Posology
The recommended starting dose is 6-9 g per day (2-3 g three times daily).

Patients previously on other phosphate binders who are switched to BindRen should start taking 6-9 g per day (2-3 g three times daily).

Dose titration
Serum phosphorus concentrations should be monitored. If an acceptable serum phosphorus concentration is not achieved, the dose may be increased by 3 g per day (1 g three times daily) in 2-3 weekly intervals. The maximum daily dose of BindRen tested in clinical trials was 15 g per day (5 g three times daily).

Special populations
Elderly population
Experience from clinical studies in patients above the age of 75 years is very limited.

Renal impairment
BindRen is indicated for use in patients with Chronic Kidney Disease (CKD) Stage 5 receiving haemodialysis or peritoneal dialysis. No data on the use of BindRen in pre-dialysis patients are available.

Severe hepatic impairment
Patients with severe hepatic impairment were excluded from clinical studies. Therefore, the use of BindRen is not recommended in patients with severe hepatic impairment (see also section 4.4). No data are available.

Paediatric population

The safety and efficacy of BindRen in children and adolescents aged under 18 years has not yet been established. No data are available.

Method of administration
BindRen is for oral use. Granules should be taken whole as one dose from the sachet.
The daily dose of BindRen granules should be taken in three equally divided doses with or immediately after meals with a sufficient amount of water to aid swallowing.
The division of the daily dose may be adjusted on a physician's advice taking into account the dietary intake of phosphate. Patients should be encouraged to adhere to their prescribed low phosphate diets.
Treatment of high blood phosphorus levels usually requires long-term treatment.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Bowel obstruction.

4.4 Special warnings and precautions for use

The safety and efficacy of BindRen has not been studied in patients with:
- Dysphagia or swallowing disorders
- Severe gastrointestinal disorders such as chronic or severe constipation, intestinal stenosis, intestinal diverticulum, sigmoid colitis, gastrointestinal ulcers, or recent major gastrointestinal surgery
- Biliary obstruction
- Severe hepatic impairment (see also section 4.2)
- Seizure disorders
- Recent history of peritonitis in peritoneal dialysis patients
- Serum albumin <30 g/L

Therefore, the use of BindRen is not recommended in patients with these disorders.

Hyperparathyroidism
BindRen alone is not indicated for the control of hyperparathyroidism.

Intestinal obstruction and ileus/subileus
In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with BindRen. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with BindRen. In patients who develop severe constipation or other severe gastrointestinal symptoms, alternative treatment may need to be considered.

Gastrointestinal haemorrhage
Caution should be exercised when treating patients with conditions which predispose to gastrointestinal haemorrhage, such as recent history of gastrointestinal haemorrhage, gastrointestinal ulcers, gastritis, diverticulosis, colitis and haemorrhoids.

Hypocalcaemia/hypercalcaemia
Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. BindRen does not contain calcium, and has no effect on serum calcium concentrations on treatment for up to one year. Serum calcium concentrations should be monitored as a normal follow-up of a dialysis patient. Elemental calcium should be given as a supplement in case of hypocalcaemia.

Fat-soluble vitamins
BindRen did not induce any clinically relevant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption syndromes and patients treated with coumarin anticoagulants (e.g. warfarin). In these patients, monitoring of vitamin A, D and E concentrations or assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.

Folate deficiency
BindRen did not induce a clinically relevant reduction in folate absorption during clinical studies of up to one year. However, intestinal folate absorption may be impaired during long-term treatment of BindRen. In these patients, monitoring serum folate status and supplementation with folic acid should be considered.

Hypothyroidism
Close monitoring of patients with hypothyroidism is recommended when levothyroxine is co-administered with BindRen (see section 4.5).

Systemic ion balance
BindRen binds phosphate and bile acid, with the release of chloride which is available for systemic absorption. Changes in systemic ion balance with an increase in chloride and decrease in bicarbonate are therefore possible. However, BindRen did not induce any clinically relevant change in chloride and bicarbonate on treatment for up to one year.

4.5 Interaction with other medicinal products and other forms of interaction

BindRen is not absorbed from the gastrointestinal tract but may affect the bioavailability or absorption rate of other medicinal products. In addition, reduced bioavailability of other medicinal products by changes in enterohepatic circulation, for example, steroid hormones with potential impairment of the effectiveness of oral contraceptives, have been reported for medicinal products with a similar mechanism of action to BindRen. When administering any medicinal product where a reduction in the bioavailability could have a clinically relevant effect on safety or efficacy, the medicinal product should be administered at least 1 hour before, or 3 hours after taking BindRen. Concomitant treatment with medicinal products with a narrow therapeutic window requires close monitoring of drug concentrations or adverse reactions, on initiation or dose-adjustment of either BindRen or the concomitant medicinal product.

Interaction studies have been conducted in healthy volunteers. Interactions have not been studied at doses >9 g daily, and greater interaction effects at higher doses of BindRen cannot be excluded.

Single dose interaction studies demonstrated that the bioavailability of ciprofloxacin, warfarin and enalapril were not affected when co-administered with BindRen (6-9 g/day). BindRen lowered the bioavailability of digoxin by 16% and C_{max} by 17%, and the C_{max} of enalapril by 27%.

Due to the high *in vitro* binding potential between BindRen and levothyroxine, closer monitoring of thyroid stimulating hormone (TSH) levels in patients receiving BindRen and levothyroxine is recommended.

No *in vivo* data are available on the possible interaction of BindRen on the absorption of the immunosuppressant medicinal products mycophenolate mofetil, ciclosporin or tacrolimus. However, decreased blood concentrations have been reported for medicinal products with a similar mechanism of action to BindRen. Caution should be exercised when prescribing BindRen to patients receiving immunosuppressants.

Patients with seizure disorders were excluded from clinical trials with BindRen. Caution should be exercised when prescribing BindRen to patients also taking anti-seizure medicinal products.

4.6 Fertility, pregnancy and lactation

BindRen is not absorbed and is not systemically available. No direct effects of BindRen are thus anticipated. However, other effects of BindRen may affect pregnant and breast-feeding women or influence fertility, see sections 4.4 and 4.5.

Pregnancy
No data are available to assess the safety and efficacy in pregnant women.
Patients that become pregnant and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.

Breast-feeding
No data are available to assess the safety and efficacy in breast-feeding women.
Patients that breast-feed and where a benefit/risk assessment confirms continued treatment with BindRen, supplementation of vitamins may be required, see section 4.4.

Fertility
No data are available to assess the potential influence of BindRen on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The Phase II and III clinical studies involving 1,410 patients with CKD Stage 5 on dialysis treated with BindRen for up to one year constituted the safety population. Patients received doses of up to 15 g per day, in three divided doses of 5 g.

Approximately 30% of patients experienced at least one adverse reaction. The most serious adverse reactions were gastrointestinal haemorrhage (uncommon) and constipation (common). The most frequently reported adverse reactions were nausea, dyspepsia and vomiting (all common). The frequency of adverse reactions increased with dose.

Tabulated list of adverse reactions
A tabulated list of frequencies was 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations	
Uncommon:	Gastroenteritis
Endocrine disorders	
Uncommon:	Hyperparathyroidism
Metabolism and nutrition disorders	
Common:	Hypocalcaemia, decreased appetite
Uncommon:	Folate deficiency, hypertriglyceridaemia, polydipsia
Rare:	Vitamin K deficiency, calciphylaxis, electrolyte imbalance, fluid overload
Psychiatric disorders	
Uncommon:	Insomnia
Nervous system disorders	
Uncommon:	Tremor, dizziness, headache, dysgeusia
Cardiac disorders	
Rare:	Coronary artery disease
Vascular disorders	
Uncommon:	Haematoma, hypotension
Gastrointestinal disorders	
Common:	Constipation, abdominal pain, vomiting, abdominal distension, nausea, gastritis, dyspepsia, diarrhoea, flatulence,

	abdominal discomfort
Uncommon:	Gastrointestinal haemorrhage, oesophagitis, faecaloma, dysphagia, change in bowel habit, dry mouth
Rare:	Intestinal obstruction*
Hepatobiliary disorders	
Uncommon:	Hepatic enzymes increased
Skin and subcutaneous tissue disorders	
Uncommon:	Urticaria, rash, pruritus, dry skin
Rare:	Allergic dermatitis, guttae psoriasis
Musculoskeletal and connective tissue disorders	
Uncommon:	Muscle spasm, musculoskeletal pain, arthralgia, back pain, pain in extremities
General disorders and administration site conditions	
Uncommon:	Asthenia

*A single case with a fatal outcome

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

BindRen has been given to dialysis patients in doses up to 15 g/day for up to one year continuously with no cases of overdose. The potential risk of overdosing could include adverse reactions or a worsening of adverse reactions mentioned in section 4.8.

There are no known antidotes to BindRen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned

BindRen contains colestilan. Colestilan is a non-absorbed, non-calcium, non-metallic phosphate-binding polymer. The binding sites become partially protonated in the stomach and interact through ionic and hydrogen bonding with both dietary phosphate anions and bile acids in the duodenum. By binding phosphate from food in the digestive tract, colestilan lowers the serum phosphorus concentration. Colestilan also binds bile acids, thereby lowering the serum LDL-cholesterol concentration. Changes in the bile acid pool in the gastrointestinal tract have also been observed to lower serum glucose. Colestilan may also bind uric acid in the gastrointestinal tract.

Three Phase III studies and two long term follow-up studies have been performed in patients with CKD Stage 5 on dialysis, in order to investigate efficacy and safety in this population.

Serum phosphorus
Fixed-dose study:
In a double-blind, 12-week fixed-dose study with five colestilan groups (3, 6, 9, 12 and 15 g/day) and placebo, colestilan at 6 g/day and above demonstrated a dose-dependent reduction in serum phosphorus level.

The least squares mean reduction from baseline to week 12 as compared to placebo was 0.16, 0.21, 0.19 and 0.37 mmol/L at 6, 9, 12 and 15 g/day respectively.

Flexible-dose studies:
Two similar 12-week, open-label, flexible-dose studies followed by a 4-week double-blind withdrawal period (comparison to placebo) were performed. In the first study, the mean serum phosphorus level was 2.33 mmol/L at baseline and 1.96 mmol/L (mean reduction by 0.36 mmol/L) at week 12 on a colestilan mean daily dose of 11.5 g. Similarly in the second study, the mean serum phosphorus level was 2.44 mmol/L at baseline and 1.94 mmol/L at week 12 (mean reduction by 0.50 mmol/L) on a colestilan mean daily dose of 13.1 g. The rate of responders (either a reduction in serum phosphorus ≤ 1.78 mmol/L and/or a reduction from baseline ≥ 0.3 mmol/L) was 50.4 % and 43.8% in the two studies, respectively (placebo 30.8% and 26.3%, respectively).

Long-term studies:
Two long-term, open-label, flexible-dose studies demonstrated that serum phosphorus reduction was maintained for up to one year. After one year, the mean serum phosphorus level was 1.89 mmol/L with a significant reduction from baseline of 0.39 mmol/L and responder rate (phosphorus level <1.78 mmol/L) was 44%. A majority of patients received 12 or 15 g/day of colestilan in the long-term studies.

Serum calcium
In clinical studies, colestilan had no effect on serum calcium levels over a period of up to one year.

Serum calcium-phosphorus ion product
Calcium-phosphorus ion product was reduced by at least 0.48 $mmol^2/L^2$ at week 12 compared to placebo at doses ≥9 g/day in fixed-dose study and by 1.05 and 0.86 $mmol^2/L^2$ at week 12 in two flexible-dose studies. Colestilan reduced calcium-phosphorus ion product by 0.90 $mmol^2/L^2$ after one year.

Serum parathyroid hormone (PTH)
In most clinical studies, colestilan decreased serum PTH compared to baseline, and was statistically significant against placebo.

Serum cholesterol
Colestilan significantly reduced serum LDL-cholesterol by 17.8, 25.6, 29.4, 34.8 and 33.4% at 3, 6, 9, 12 and 15 g/day at week 12 compared to placebo in fixed-dose study, respectively. Colestilan also showed significant reductions from baseline by 35.3 and 30.1% at week 12 in two flexible-dose studies, and by 25.8% after one year in long-term studies. The reductions in LDL-cholesterol are also reflected in significant falls in total cholesterol.

Serum glycosylated haemoglobin A1c
In subjects with baseline HbA1c ≥7.0%, colestilan showed a reduction of between 0.36 to 1.38% at week 12 in the fixed-dose study, and by 0.94 and 0.91% at week 12 in the two flexible-dose studies. After one year of treatment, a reduction of 1.12% in HbA1c was observed.

Serum uric acid
Colestilan was also associated in dose-dependent reduction in serum uric acid, with a mean reduction of 43 micromol/L after one year of treatment.

5.2 Pharmacokinetic properties

BindRen is not absorbed from the gastrointestinal tract of healthy volunteers following oral administration of ^{14}C-radiolabelled colestilan.

The results of *in vitro* testing suggest that medicinal products with anionic and/or lipophilic characteristics have a higher potential to bind to BindRen.

5.3 Preclinical safety data

Non-clinical data reveal no direct special hazard for humans based on conventional studies of safety pharmacology, single- and repeated-dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development. However, reproductive toxicity studies were not conducted at doses higher than 2.5 times the human clinical dose, and the possible reproductive effects related to coagulation and bleeding have not been assessed.

Haemorrhage and increased clotting parameters (PT and aPTT) were evident in rats following repeat administration. These were considered to result from a deficiency of vitamin K following a reduction in the absorption of fat-soluble vitamins (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granule core
Purified water
Hydroxypropylcellulose
Silica, colloidal anhydrous
Castor oil, hydrogenated

Film-coating
Ethylcellulose
Hypromellose
Macrogol 8000
Triethyl citrate
Titanium dioxide
Talc
Cetyl alcohol
Sodium laurilsulfate
Castor oil, hydrogenated

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Foil laminate (polyethylene terephthalate/polyethylene/aluminium foil/polyethylene/polyvinylidene chloride) sachets.
Each sachet contains 3 g of granules.

Pack sizes:
30, 60 or 90 sachets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Mitsubishi Pharma Europe Ltd.
Dashwood House
69 Old Broad Street
London
EC2M 1QS
United Kingdom

Tel: +44 (0)207 065 5000
Fax: +44 (0)207 065 5050
Email: information@mitsubishi-pharma.eu

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/014-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 2013

10. DATE OF REVISION OF THE TEXT

8 August 2013

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 responsible for batch release

allphamed PHARBIL Arzneimittel GmbH
Hildebrandstr. 12
37081 Göttingen
Germany

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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTERS - FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

BindRen 1 g film-coated tablets
colestilan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 g colestilan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

45 film-coated tablets
99 film-coated tablets
198 film-coated tablets
270 film-coated tablets
297 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

9. SPECIAL STORAGE CONDITIONS

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

Mitsubishi Pharma Europe Ltd.
Dashwood House
69, Old Broad Street
London
EC2M 1QS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/006-010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BindRen 1 g tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS – FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

BindRen 1 g film-coated tablets
colestilan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mitsubishi Pharma Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - 2 G GRANULES IN SACHETS

1. NAME OF THE MEDICINAL PRODUCT

BindRen 2 g granules
colestilan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 2 g colestilan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Granules
30 sachets
60 sachets
90 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

9. SPECIAL STORAGE CONDITIONS

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

Mitsubishi Pharma Europe Ltd.
Dashwood House
69, Old Broad Street
London
EC2M 1QS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/011-013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BindRen 2 g granules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - 3 G GRANULES IN SACHETS

1. NAME OF THE MEDICINAL PRODUCT

BindRen 3 g granules
colestilan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 3 g colestilan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Granules
30 sachets
60 sachets
90 sachets

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

9. SPECIAL STORAGE CONDITIONS

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

Mitsubishi Pharma Europe Ltd.
Dashwood House
69, Old Broad Street
London
EC2M 1QS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/014-016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BindRen 3 g granules

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET FOR 2 G GRANULES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BindRen 2 g granules
colestilan
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 g

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET FOR 3 G GRANULES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

BindRen 3 g granules
colestilan
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 g

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BOTTLES – FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

BindRen 1 g film-coated tablets
colestilan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 g colestilan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

45 film-coated tablets
99 film-coated tablets
198 film-coated tablets
270 film-coated tablets
297 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

9. SPECIAL STORAGE CONDITIONS

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

Mitsubishi Pharma Europe Ltd.
Dashwood House
69, Old Broad Street
London
EC2M 1QS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/804/001-005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BindRen 1 g tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE LABEL – FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

BindRen 1 g film-coated tablets
colestilan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 g colestilan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

45 film-coated tablets
99 film-coated tablets
198 film-coated tablets
270 film-coated tablets
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B. PACKAGE LEAFLET

Package leaflet: Information for the patient

BindRen 1 g film-coated tablets
colestilan

▼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, pharmacist or nurse.
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What BindRen is and what it is used for
2. What you need to know before you take BindRen
3. How to take BindRen
4. Possible side effects
5. How to store BindRen
6. Contents of the pack and other information

1. What BindRen is and what it is used for

BindRen contains the active substance colestilan. It is used to lower high blood phosphorus levels in adult patients undergoing dialysis due to poor kidney function.

About high blood phosphorus levels (hyperphosphataemia)
If your kidneys no longer function properly you may undergo dialysis, which replaces many of the functions of your kidneys. You have also been advised to follow a special diet to reduce the amount of phosphorus that your body takes from food. Sometimes, the dialysis and diet are not enough to stop the phosphorus in your blood rising to high levels, a condition referred to by your doctor as hyperphosphataemia. Keeping the phosphorus level in your blood low is important to maintain healthy bones and blood vessels and to prevent itchy skin, red eyes, bone pain or bone fractures.

How BindRen works
Colestilan binds to the phosphorus from food in your digestive tract to prevent it from being absorbed into your blood. The colestilan-bound phosphorus is then excreted from your body in faeces. However, even though you are taking BindRen, you must also follow the special diet recommended by your doctor.

2. What you need to know before you take BindRen

Do not take BindRen
- if you are allergic to colestilan or any of the other ingredients of this medicine (listed in section 6)
- if you have bowel obstruction (a blockage of your intestines)

Warning and precautions
Talk to your doctor or pharmacist before taking BindRen if you are suffering from any of the following problems, since this medicine may not be right for you:
- swallowing problems
- severe problems with stomach or bowel movement, such as constipation, ulcers in the stomach or the gut or haemorrhoids, since these problems may lead to increased risk of e.g. bleeding from the intestines
- recent major stomach or bowel surgery
- gall bladder obstruction
- severe liver problems
- seizures
- recent history of inflammation of the membrane that forms the lining of the abdominal (tummy) cavity (peritonitis)
- low levels of albumin (a protein) in your blood

Talk to your doctor or pharmacist if during your treatment with BindRen, any of the following applies to you:
- you experience constipation, since your doctor may wish to monitor your bowel function to detect potential side effects (see section 4).
- you have been told that you have a disorder that decreases the intestines ability to absorb nutrients (malabsorption syndrome) or if you are treated with so called coumarin anticoagulants (e.g. warfarin), since your doctor may want to monitor your blood and possibly ask you to start taking vitamin supplements.
- you have abnormally low levels of calcium in your blood. BindRen does not contain calcium and your doctor may prescribe additional calcium tablets.
- you have abnormally high levels of calcium in your blood due to overactivity of the parathyroid glands. BindRen alone cannot treat this condition and other medicines should be prescribed for you.

Children and adolescents
No data are available on the safety and effectiveness of BindRen in children and adolescents (below the age of 18 years). BindRen should not be used in children and adolescents.

Other medicines and BindRen
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines for irregular heart rhythm (such as digoxin), for treating high blood pressure (such as enalapril maleate), anti-seizure medicines (such as valproic acid, phenytoin, carbamazepine, lamotrigine, oxcarbazepine, topiramate, gabapentin, vigabatrin, zonisamide and levetiracetam), levothyroxine (used to treat thyroid hormone deficiency), oral birth control medicines (oestrogen, progestogen or combination pills), immune system suppressing medicines (such as cyclosporine, mycophenolate mofetil, tacrolimus). This is because your doctor may want to monitor your health, change the dose of BindRen or the other medicine you are taking or tell you to not take BindRen and the other medicine at the same time.

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 for advice before taking this medicine. If you do become pregnant or you are breast-feeding, and your doctor decides that you should continue your treatment with BindRen, your doctor may ask you to also take vitamin supplements.

Driving and using machines
BindRen has no or negligible influence on the ability to drive or use machines.

3. How to take BindRen

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

The recommended starting dose is 6-9 g per day taken as 2 g or 3 g three times per day with meals. Your doctor may decide to increase this up to a total dose of 15 g per day depending on the level of phosphorus in your blood. If you do not regularly eat three meals per day then please tell your doctor.

Take BindRen by mouth.
It is recommended that you take the tablets whole with meals and with a small amount of water.
Your doctor may advise you to take calcium, vitamin D supplements and other vitamins or other medicines in addition to BindRen.

If you have to take other medicines your doctor will tell you if you can take the other medicines at the same time as BindRen or if you need to take the other medicines 1 hour before or 3 hours after taking BindRen. Your doctor may consider measuring blood levels of the other medicines you are taking.

If you take more BindRen than you should
If you take too much BindRen, tell your doctor or pharmacist.

If you forget to take BindRen
Do not take a double dose to make up for forgotten doses. Just carry on with the next dose at the normal time.

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

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 most serious side effects are bleeding from the stomach or lower bowel (uncommon). This may show as either fresh or altered blood in your vomit, or when from the lower bowel, as a black stool or with blood mixed in your stool.

Constipation is common and if you suffer from persistent or worsening constipation please tell your doctor or pharmacist as this may be the first sign of blockage of your intestines.

The following side effects have also been seen in patients taking BindRen:

Common (may affect up to 1 in 10 people) side effects: feeling sick (nausea), vomiting, a burning sensation in your stomach, diarrhoea, bloating, stomach ache and bowel pain, gas, a decreased appetite and low blood calcium.

Uncommon (may affect up to 1 in 100 people) side effects: low blood pressure, weakness, thirst, headache, dizziness, shaking, dry mouth, swallowing difficulties, change in taste sensation, heartburn, hardening of the stool, inflammation or pain of the stomach or bowel, change in bowel habit, sleeplessness, itching, dry skin, rash, hives, itching red spots, collection of blood (haematoma) e.g. under the skin, joint pain, back pain, pain in limbs, muscle pain or spasms, increased blood levels of parathyroid hormone (a protein), certain blood fats and liver enzymes and a low level of folate (a vitamin).

Rare (may affect up to 1 in 1000 people) side effects: blockage of intestines, a low level of vitamin K, obstruction of the blood vessels that supply the heart muscle and swelling of the ankles or extremities.

Reporting of side effects

If you get any side effects, talk to you 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 BindRen

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

Do not use this medicine after the expiry date stated on the box, the bottle label or the blister after the abbreviation "EXP". The expiry date refers to the last day of that month.

Blisters
This medicine does not require any special storage conditions.

Bottles
This medicine does not require any special temperature storage conditions.
Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment and to prevent accidental access by children.

6. Contents of the pack and other information

What BindRen contains

The active substance is colestilan.

Each film-coated tablet contains 1 g of colestilan.

The other ingredients are purified water, hydroxypropylcellulose, colloidal, anhydrous silica, hydrogenated castor oil, hypromellose, acetic acid esters of mono- and diglycerides of fatty acids, polysorbate 80, shellac, indigo carmine aluminium lake (E132) and carnauba wax.

What BindRen looks like and contents of the pack

BindRen tablets are white oval shaped film-coated tablets printed with "BINDREN" in blue ink on one side. They are supplied in blisters or bottles in cartons of 45, 99, 198, 270 or 297 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer
allphamed PHARBIL Arzneimittel GmbH
Hildebrandstr. 12

37081 Göttingen
Germany

For more information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Med-info@mitsubishi-pharma.eu

This leaflet was last revised in 08/2013

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

Package leaflet: Information for the patient

BindRen 2 g granules
BindRen 3 g granules
colestilan

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What is in this leaflet

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3. How to take BindRen
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1. What BindRen is and what it is used for

BindRen contains the active substance colestilan. It is used to lower high blood phosphorus levels in adult patients undergoing dialysis due to poor kidney function.

About high blood phosphorus levels (hyperphosphataemia)
If your kidneys no longer function properly you may undergo dialysis, which replaces many of the functions of your kidneys. You have also been advised to follow a special diet to reduce the amount of phosphorus that your body takes from food. Sometimes, the dialysis and diet are not enough to stop the phosphorus in your blood rising to high levels, a condition referred to by your doctor as hyperphosphataemia. Keeping the phosphorus level in your blood low is important to maintain healthy bones and blood vessels and to prevent itchy skin, red eyes, bone pain or bone fractures.

How BindRen works
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2. What you need to know before you take BindRen

Do not take BindRen
- if you are allergic to colestilan or any of the other ingredients of this medicine (listed in section 6)
- if you have bowel obstruction (a blockage of your intestines)

Warning and precautions
Talk to your doctor or pharmacist before taking BindRen if you are suffering from any of the following problems:

- swallowing problems
- severe problems with stomach or bowel movement, such as constipation, ulcers in the stomach or the gut or haemorrhoids, since these problems may lead to increased risk of e.g. bleeding from the intestines
- recent major stomach or bowel surgery
- gall bladder obstruction
- severe liver problems
- seizures
- recent history of inflammation of the membrane that forms the lining of the abdominal (tummy) cavity (peritonitis)
- low levels of albumin (a protein) in your blood

Talk to your doctor or pharmacist if during your treatment with BindRen, any of the following applies to you:
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- you have been told that you have a disorder that decreases the intestines ability to absorb nutrients (malabsorption syndrome) or if you are treated with so called coumarin anticoagulants (e.g. warfarin), since your doctor may want to monitor your blood and possibly ask you to start taking vitamin supplements.
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3. How to take BindRen

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

The recommended starting dose is 6-9 g per day taken as 2 g or 3 g three times per day with meals. Your doctor may decide to increase this up to a total dose of 15 g per day depending on the level of phosphorus in your blood. If you do not regularly eat three meals per day then please tell your doctor.

Take BindRen by mouth.
It is recommended that you take BindRen granules as one dose from the sachet with a small amount of water, at the time of a meal or directly after. However, if you cannot swallow the contents of a whole sachet at once you can divide the contents of the sachet dose into smaller portions.

Your doctor may advise you to take calcium, vitamin D supplements and other vitamins or other medicines in addition to BindRen.

If you have to take other medicines your doctor will tell you if you can take the other medicines at the same time as BindRen or if you need to take the other medicines 1 hour before or 3 hours after taking BindRen. Your doctor may consider measuring blood levels of the other medicines you are taking.

If you take more BindRen than you should
If you take too much BindRen, tell your doctor or pharmacist.

If you forget to take BindRen
Do not take a double dose to make up for forgotten doses. Just carry on with the next dose at the normal time.

If you stop taking BindRen
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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 most serious side effects are bleeding from the stomach or lower bowel (uncommon). This may show as either fresh or altered blood in your vomit, or when from the lower bowel, as a black stool or with blood mixed in your stool.

Constipation is common and if you suffer from persistent or worsening constipation please tell your doctor or pharmacist as this may be the first sign of blockage of your intestines.

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5. How to store BindRen

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

Do not use this medicine after the expiry date stated on the box or the sachet after the abbreviation "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment and to prevent accidental access by children.

6. Contents of the pack and other information

What BindRen contains

The active substance is colestilan.
- BindRen 2 g granules: each sachet contains 2 g of colestilan.
- BindRen 3 g granules: each sachet contains 3 g of colestilan.

The other ingredients are: purified water, hydroxypropylcellulose, colloidal, anhydrous silica, hydrogenated castor oil, ethylcellulose, hypromellose, macrogol 8000, triethyl citrate, titanium dioxide, talc, cetanol and sodium laurilsulfate.

What BindRen looks like and contents of the pack

BindRen granules are white cylindrical granules. They are supplied in 2 g or 3 g sachets in cartons of 30, 60 or 90 sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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