SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Osvaren 435 mg / 235 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Calcium acetate, 435 mg equivalent to 110 mg calcium and Magnesium carbonate, heavy 235 mg equivalent to 60 mg magnesium

Excipients with known effect
Each film-coated tablet contains 5.6 mg sodium and 50 mg sucrose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to yellowish, oblong film-coated tablet with a single score line.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of hyperphosphatemia associated with chronic renal insufficiency in patients undergoing dialysis (haemodialysis, peritoneal dialysis).

OsvaRen is indicated in adults.

4.2. Posology and method of administration

Posology

Adults
3 to 10 film-coated tablets per day, depending on the serum phosphate level. The daily dose should be subdivided according to the number of meals per the day (usually 3 a day).

The recommended starting dose is 3 tablets daily.

If necessary, the dosage may be raised to maximally 12 film-coated tablets per day.

Paediatric population
The safety and efficacy of OsvaRen in children and adolescence have not been established. Therefore, the administration of OsvaRen is not recommended in children and adolescents below 18 years of age (see section 4.4)

Method of administration

To achieve the maximum phosphate binding effect, OsvaRen must be taken together with the meal and should not be crushed or chewed.

For easy swallowing, the tablets should be taken together with some liquid.

In case the tablets are too large to be swallowed by the patient, the tablets should be broken along the score line immediately before swallowing in order to avoid the development of taste of acetic acid.

Because the rate and/or extent of absorption of other defined medicinal products may vary when used concomitantly with OsvaRen, none of the oral medicinal products listed in section 4.5 should be taken within the period 2 hours before and 3 hours after administration of OsvaRen (see section 4.5).

OsvaRen can be applied long-term.

4.3. Contraindications

OsvaRen is contraindicated in patients with:

- Hypophosphataemia
- Hypercalcaemia with or without clinical symptoms, e.g. as a result of an overdose of vitamin D, a paraneoplastic syndrome (bronchial carcinoma, breast cancer, renal cell carcinoma, plasmacytoma), bone metastases, sarcoidosis or immobilisation osteoporosis;
- Elevated serum magnesium levels of more than 2 mmol/l, and/or symptoms of hypermagnesaemia;
- AV-block III°;
- Myasthenia gravis;
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

The use of phosphate binders should be preceded by a dietary consultation with the patient concerning phosphate uptake, and may depend on the kind of dialysis treatment the patient is receiving.

OsvaRen should only be administered with caution (only with continuous monitoring of serum calcium, magnesium and phosphate) in case of severe hyperphosphataemia with a calcium-phosphate-product of more than 5.3 mmol2/l2 if

- refractory to therapy,
- refractory hyperkalaemia,
- clinical relevant bradycardia or AV-block II° with bradycardia.

Continuous monitoring of serum phosphate, serum magnesium, serum calcium and the calcium-phosphate-product should be performed, especially in case of simultaneous intake of vitamin D preparations and thiazide diuretics.
High doses and long-term administration of OsvaRen may result in hypermagnesaemia. Hy-permagnesaemia is mostly asymptomatic, but in some cases systemic effects may be seen.
For symptoms and management of hypermagnesaemia and hypercalcaemia please see section 4.9.

Patients should be advised to seek medical advice before taking antacids containing calcium or mag-nesium salts to avoid adding to the calcium or magnesium load.

If patients with a chronic renal insufficiency receive OsvaRen they may develop hypercalcaemic episodes, especially in combination with the administration of metabolites of vitamin D.

Patients should be warned of the possible symptoms of hypercalcaemia.

During a long-term therapy with OsvaRen attention must be paid to the progression or the appearance of vascular and soft tissue calcifications. The risk decreases by lowering the calcium-phosphate-product to < 4.5 mmol2/l2.

In patients receiving digitalis glycosides, OsvaRen should only be administered under ECG control and monitoring of the serum calcium level.

Increased intake of calcium salts may result in the precipitation of fatty acids and bile acid as calcium soap. This may lead to constipation.

In case of diarrhoea the dosage of OsvaRen should be reduced.

OsvaRen contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

OsvaRen contains sodium. This has to be taken in consideration by patients on a controlled sodium diet.

Paediatric population
The safety and efficacy of OsvaRen in children and adolescence have not been established. There-fore, the administration of OsvaRen is not recommended in children and adolescents below 18 years of age.

4.5. Interaction with other medicinal products and other forms of interaction

To prevent an interaction between OsvaRen and other defined medicinal products when taken con-comitantly, none of the oral medicinal products listed in this section should be taken within the period 2 hours before and 3 hours after administration of OsvaRen (see section 4.2).

OsvaRen affects the absorption of antibiotics (such as tetracyclines, doxycycline, norfloxacin, some cephalosporins like cefpodoxime, cefuroxime, and some quinolones (gyrase inhibitors) like ciproflox-acin), biphosphonates, fluorides, ketokonazole, estramustin-preparation, anticholinergics, zinc, urso- and chenodesoxychol acid, halofantrine, , .

In case of an additional treatment with oral iron preparations, attention has to be paid to the fact that simultaneous intake of magnesium may influence iron absorption.

Magnesium salts may adsorb digoxin in the gastrointestinal tract, decreasing its bioavailability.
Adsorption of nitrofurantoin may occur, decreasing the bioavailability and possibly the anti-infective effect of this medicinal product.
Further, the gastrointestinal absorption of penicillamine may be decreased, possibly decreasing its pharmacological effects.

A combination of magnesium carbonate, hydroxide and aluminium hydroxide with levothyroxine may cause an increased absorption of levothyroxine.

Vitamin D and derivatives increase the absorption of calcium. Thiazide diuretics reduce the renal elimination of calcium. In case of a simultaneous administration of OsvaRen and thiazides or vitamin D derivatives it is therefore necessary to control the serum calcium level (see section 4.4).

Concurrent use of oestrogens with OsvaRen may increase calcium absorption.

The sensitivity for glycosides and therefore the risk for arrhythmia is increased by elevated serum calcium levels (see section 4.4).
The administration of adrenalin in patients with increased serum calcium levels may lead to severe arrhythmia.
The effect of calcium antagonists may be reduced.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of OsvaRen in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). OsvaRen should not be used during pregnancy unless the clinical condition of the woman requires treatment with calcium acetate and magnesium carbonate

Breastfeeding
Calcium acetate and magnesium carbonate are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely (see section 5.2). Breast-feeding is not recommended during treatment with OsvaRen.

Fertility
No data available.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

Very common (≥1/10)
Common (≥ 1/100 and <1/10)
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000 and <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Gastrointestinal disorders:
Common:
Soft stools, gastrointestinal irritation like nausea, anorexia, sensation of fullness, belching and constipation, diarrhoea.

Metabolism and nutrition disorders:
Common:
Hypercalcaemia either asymptomatic or symptomatic, asymptomatic hypermagnesaemia.

Uncommon:
Moderate to severe symptomatic hypercalcaemia, symptomatic hypermagnesaemia.

Very rare:
Hyperkalaemia, magnesium-induced osteal mineralisation disturbances.

For symptoms of hypercalcaemia and hypermagnesaemia see section 4.9.

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 profes-sionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9. Overdose

An acute hypermagnesaemia (either asymptomatic or with acute systemic toxicity) suppresses both the central and the peripheral neural activity by inhibiting acetylcholine release. Systemic toxicity is to be expected from a serum concentration of 2.5 mmol/l, severe neurotoxic side effects appear from 3 mmol/l and above. With concentrations of 2.5 – 5.0 mmol/l gastrointestinal disturbances (nausea, anorexia,

constipation), cystospasm, muscle weakness, lethargy, missing deep-tendon reflexes and disturbed AV-conduction and ventricular stimulus conduction has been observed. In case of serum magnesium levels of 5 – 10 mmol/l, arterial hypotension induced by vasodilatation, paralytic ileus, flaccid paralysis and coma have been observed. At a level of more than 10 mmol/l respiratory arrest and cardiac arrest occur.

Symptoms of hypercalcaemia are initially muscle weakness and gastrointestinal disturbances (ab-dominal pain, constipation, nausea and vomiting). Severe hypercalcaemia is characterised by disturb-ances of consciousness (e.g. lethargy, disorientation, stupor, in extreme cases also coma). In patients with a serum calcium level of more than 3.5 mmol/l a hypercalcaemic crisis is possible with the symptoms of:

- Polyuria, polydipsia
- Nausea, anorexia, constipation, pancreatitis (infrequent)
- Arrhythmia, shortening of the QT-interval, adynamia, hypertension
- Muscle weakness up to pseudo paralysis
- Psychosis, somnolence up to coma.

Long-term overdosing may lead to the development of an adynamic osteopathy.

Emergency treatment:
In addition to symptomatic treatment, the therapy of hypermagnesaemia consists in lowering the magnesium-concentration of the dialysate and in a reduction of the dose of OsvaRen.

If serum calcium levels increase to more than 2.5 mmol/l, a dose reduction and/or a decrease of the dialysate calcium to 1.25 mmol/l should be considered beside the symptomatic treatment. In the event of a hypercalcaemia (serum calcium > 2.75 mmol/l) the therapy with OsvaRen should be temporarily withdrawn. In patients with a serum calcium level of more than 3.5 mmol/l the therapeutic intervention consists of a haemodialysis treatment with calcium-free dialysate. During the treatment with a calcium-free dialysate close monitoring of serum calcium concentration is necessary in order to minimise the risk of hypocalcaemia and adverse cardiovascular reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalemia and hyperphosphatemia, ATC-Code: V03AE04

Mechanism of action
As calcium acetate and magnesium carbonate are phosphate-binding compounds, they lead together with the phosphate contained in food to the formation of low solubility calcium and magnesium phosphate-salts in the gut, which then will be excreted with the faeces. Calcium acetate reaches its maximal phosphate-binding capacity at a pH of 6 – 8. Therefore, OsvaRen is also suitable for phosphate binding in patients with hypo- or anacidity of the stomach.

5.2. Pharmacokinetic properties

Absorption
Provided that no precipitation to magnesium complexes is caused by dietary phosphate or other nutrients, the dissolved magnesium ions are bioavailable and are absorbed in the intestine.

The absorption of orally administered magnesium in healthy humans depends on the supply. Experi-ments have shown that the rate of absorption in patients who received 1.5 mmol magnesium per day was 65 %, and in patients who received 40 mmol per day it was only 11 %.

The dissolved calcium ions are bioavailable and can be absorbed via the intestinal route as long as calcium does not form insoluble calcium complexes with the phosphate contained in food or other nutrients. Absorption of calcium is governed by hormonal regulatory mechanisms. The ratio of ab-sorption increases with higher doses and with hypocalcaemic states and decreases with increasing age. Depending on the vitamin D status and the doses taken, a fractional absorption of 10-35 % can be expected. Administration of higher doses will only result in a smaller increase of the amount absorbed. The normal daily intake with food amounts to approx. 1000 mg.

Distribution
Total body magnesium is about 20 – 28 g. In healthy adults about 53% of total body magnesium is in bone, 27 % in muscle, 19% in soft tissue and less than 1 % extracellular. The majority of intracellular magnesium is found in bound form.

Total body calcium is about 1250 g (31 mol) in a person weighting 70 kg, of which 99 % is located in bones and teeth. About 1 g is in the plasma and the extracellular fluid, and 6 to 8 g in the tissues themselves. Reference values for serum total calcium vary among clinical laboratories, depending on the methods of measurement, within a normal range of 2.15-2.57 mmol/l. About 40 to 45 % of this quantity is bound to plasma proteins, about 8 to 10% is complexed with ions such as citrate, and 45 to 50 % is dissociated as free ions.

Elimination
Orally administered magnesium salts are eliminated in the urine (absorbed fraction) and the faeces (unabsorbed fraction). Small amounts are excreted into breast-milk. Magnesium crosses the placen-ta.

Under physiologic conditions calcium is excreted in approximately equal amounts in urine and en-dogenous intestinal secretion. Parathyroid hormone, vitamin D and thiazide diuretics decrease urinary excretion of calcium, whereas other diuretics (loop diuretics), calcitonin and growth hormone promote renal excretion. Urinary calcium excretion decreases in early stages of renal failure. Urinary calcium excretion increases during pregnancy. Calcium is also excreted by the sweat glands. Calcium crosses the placenta and is excreted into breast-milk.

5.3 Preclinical safety data

Standard genotoxicity studies have not been performed with Osvaren. Based on available data no genotoxic or carcinogenic potential have to be assumed.

No reproductive toxicity studies have been performed with this medicine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Starch, pregelatinised, from maize
maize starch
sucrose
gelatin
croscarmellose sodium
magnesium stearate

Film coating:

Castor oil, refined
hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening of the container: 3 months

6.4. Special precautions for storage

Keep the container tightly closed in order to protect from moisture.
For storage conditions after first opening of the medicinal product, see section 6.3

6.5. Nature and contents of container

HDPE container with LDPE cap: Pack size of 180 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Fresenius Medical Care Nephrologica Deutschland GmbH,
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.H., Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 29386/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11.03.2008
Date of latest renewal: 03.01.2011

10 DATE OF REVISION OF THE TEXT

30/03/2017