IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1350/003/001
Case No: 2032366

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Fresenius Medical Care Nephrologica Deutschland GmbH

61346 Bad Homburg v.d.H., **Germany**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Everose 660mg film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **29/02/2008** until **28/02/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Everose 660 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 660 mg calcium acetate, equivalent to 167 mg calcium.

Excipients:
Each film-coated tablet contains 68.3 mg sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to yellowish, oblong-shaped tablet with a 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

Hyperphosphataemia in patients with chronic renal insufficiency undergoing dialysis.

4.2 Posology and method of administration

Everose should always be used with close monitoring (see section 4.4).

In adults
The recommended starting dose is two tablets (334 mg calcium) three times daily. The dose is gradually increased until the desired serum phosphorus level is reached, provided that hypercalcaemia does not occur. Most patients require 3 to 4 tablets with each meal.

The dose may need to be adjusted either upwards or downwards, depending on phosphate intake and elimination of phosphate by dialysis.

In children and adolescent (less than 18 years of age)
No sufficient information is available on the relationship of age to the effects of calcium acetate in paediatric patients. Therefore, Everose cannot be recommended in these patients.

In the elderly
Normal dosage regimen is recommended in the elderly.

The tablets should only be taken together with meals to achieve the maximum-phosphate binding effect. Preferably the tablets should be swallowed whole. When a patient has difficulty swallowing the tablet due to its size, the tablet can be broken in half on the score line if necessary, so half a tablet can be taken twice directly after each other.
In that case the tablets need to be divided into halves just before ingestion to avoid the development of taste of acetic acid.

In case of a missed dose, the next dose should be taken at the normal time (no attempt should be made to make up for the missed dose).

4.3 Contraindications

- Hypophosphataemia
- Hypercalcaemia
- Hypersensitivity to calcium acetate or to any of the excipients

4.4 Special warnings and precautions for use

Patients should be advised not to take any other oral medication within 1-2 h before and after Everose (see section 4.5).

Chronic overdose of calcium preparations in uraemic patients can cause soft tissue calcifications. The risk of hypercalcaemia is increased in cases of concomitant treatment with vitamin D- preparations.

Increased amounts of calcium salts in the gastrointestinal tract may result in the precipitation of fatty acids and bile acids as calcium salt. This may lead to constipation.

The application of adrenaline (epinephrine) in patients with increased serum calcium level may lead to severe cardiac arrhythmias.

Serum phosphorus and calcium levels should be closely monitored at regular intervals. The calcium phosphate product should not exceed 5.25 $mmol^2/l^2$, since the incidence of soft tissue calcifications increases by exceeding this value. Monitoring should be more frequent after initiation of the therapy e.g. in weekly intervals or every 2 weeks for 3 months. After this monthly intervals are sufficient, dependent on the medical condition of the patient. In general the monitoring frequency is up to the decision of the doctor and depends on the medical profile of the patient. The prolonged exceeding of a calcium phosphate product of 5.25 $mmol^2/l^2$ should prompt a therapy change.

To avoid an increase of serum calcium above normal levels, in case of a previous therapy with calcium supplements the amount of calcium that is administered with Everose should be considered.

In case of hypercalcaemia the dose should be reduced or the treatment discontinued, depending on the degree of hypercalcaemia. For the symptoms of hypercalcaemia see section 4.8.

Calcium salts should generally be avoided in patients with calcium renal calculi, or a history of renal calculi. Calcium salts should be given cautiously to patients with diseases associated with hypercalcaemia such as sarcoidosis and some malignancies.

Patients should be warned for the possible symptoms of hypercalcaemia.

In patients where there is difficulty controlling serum phosphorous concentrations e.g. with severe hyperphosphataemia (serum levels >2.26 mmol/L), aluminium based phosphate binders may be used as a short term therapy (4 weeks).

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.

This product contains sucrose. Due to the content of sucrose patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Everose
On concomitant administration of thiazide diuretics (bendroflumethiazide) or vitamin D-preparations there is an increased risk of hypercalcaemia. If these drugs are prescribed simultaneously, additional serum calcium monitoring, *eg*, weekly may be necessary, above the regular monitoring intervals as given in section 4.4.

Concurrent use of oestrogens (estradiol) or vitamin A preparations with calcium salts may increase calcium absorption.

Effects of Everose on other medicinal products
Because the rate and/or extent of absorption of other oral medications may vary when used concurrently with Everose, patients should be advised not to take any other oral medication within 1-2 h before and after Everose.
Calcium salts can form complexes with citrates, phosphates, carbonates/bicarbonates, oxalates, tartrates, phytates or sulphates. Calcium salts affect, like other multivalent cations, the absorption of numerous anionic active substances by forming poorly soluble salts. Thus, the concurrent use of calcium containing drugs with tetracyclines, bisphosphonates, fluorides, some fluoroquinolones (ciprofloxacin, ofloxacin), some cephalosporins (cefpodoxime, cefuroxime), ketoconazole, estramustin-preparations and anticholinergics may reduce the intestinal absorption of these substances. Also the intestinal absorption of zinc and iron may be reduced.

Increased amounts of calcium salts in the gastrointestinal tract may reduce the absorption of therapeutically administered urso- and chenodesoxycholic acid due to precipitation as calcium soap.

Calcium increases the effect of digitalis glycosides (digoxin), which may result in digitalis intoxication including the risk of arrhythmia. In digitalised patients care should be taken when administering Everose, e.g. ECG monitoring is warranted.

Calcium can reduce the pharmacological effects of verapamil and probably of other calcium channel blockers.

4.6 Pregnancy and lactation

For calcium acetate no clinical data on exposed pregnancies are available. Preclinical studies with respect to affect pregnancy, embryonal/foetal development, parturition and/or postnatal development have not been performed with Everose. Caution should be exercised when prescribing to pregnant women. During pregnancy, serum calcium levels should be closely monitored at regular intervals.

It is not known whether calcium acetate is distributed in breast milk. Breast-feeding is not recommended when women need Everose in that time.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1000 to <1/100)
Rare	(≥1/10 000 to <1/1000)
Very rare	(<1/10 000), not known (cannot be estimated from the available data)

Metabolism and nutrition disorders:
Common:

- *Mild* Hypercalcaemia

  Mild hypercalcaemia (Ca>2.6 mmol/l) may occur in about 1% of patients and may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting.

Uncommon:

- *More Severe Hypercalcaemia*
  More severe hypercalcaemia (Ca> 3.0 mmol/l) may occur in about 0.1% of patients and can be associated with cardiac rhythm disorders, confusion, lethargy, delirium, stupor and in very severe cases coma. Patients should be advised to consult their doctor if any of these symptoms occur.

Gastrointestinal disorders:
Common:

- nausea
- vomiting
- bloated feeling
- belching
- constipation
- diarrhoea

4.9 Overdose

Overdose may result in hypercalcaemia. Chronic overdose in uraemic patients may result in soft tissue calcification.

Emergency treatment, antidotes
In case of hypercalcaemia (serum calcium level > 2.5 mmol/l) both the dialysate calcium (to 1.25 mmol/l) and/or the dosage of Everose has to be reduced. If a serum calcium level of 2.75 mmol/l is exceeded, the administration of Everose must be temporarily interrupted and if necessary calcium-free phosphate binder has to be applied. A hypercalcaemic crisis (serum calcium level > 3.5 mmol/l) requires a therapy with a calcium free dialysate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mineral supplements, Calcium

ATC code: A 12 AA 12

Everose contains calcium acetate, and is primarily intended in patients with chronic renal failure. They cannot excrete phosphate via the kidneys to the normal degree, and this leads to hyperphosphataemia. Diet or elimination of phosphate is insufficient, and phosphate-binding substances must be used to reduce phosphate absorption in the gastrointestinal tract. Calcium acetate taken with meals, together with phosphate in the food forms poorly soluble calcium phosphate, which is excreted with faeces.

5.2 Pharmacokinetic properties

Absorption
Although this product is intended to act locally to bind phosphate in the gut, the amount of calcium involved in the binding of phosphate is variable and any unbound calcium may be absorbed in the gastrointestinal tract by active transport and passive diffusion. Calcium is actively absorbed in the duodenum and proximal jejunum, and to a lesser extent, in the more distal segment of the small intestine. After oral administration of calcium acetate, approximately 40% is absorbed in the fasting state and approximately 30% is absorbed in the non-fasting state. Calcium absorption is decreased in patients with chronic renal insufficiency, in other disease states and if calcium binds to phosphate. Any bound calcium cannot be absorbed.

Distribution
Bone contains 99% of the body calcium, the remaining 1% is distributed equally between the intra- and extracellular fluids. Of the total serum calcium concentration, 50% is in the ionic form and 5% is complexed by phosphates, citrates and other anions. Approximately 45% of the serum calcium is bound to plasma proteins.

Metabolism
The anion of calcium acetate (acetate ion) is a metabolite of glucose metabolism. Bound to the sulfydryl group of coenzyme A it can be catabolised in the citrate cycle and as well in many other metabolic pathways. Absorbed acetate is rapidly metabolised to bicarbonate.

Excretion
Under physiologic conditions about 90% of the daily intake of calcium is excreted in the faeces, approximately 10% of the ingested calcium is excreted in the urine. Urinary calcium excretion decreases during development of renal failure.

5.3 Preclinical safety data

Preclinical studies with calcium acetate are very limited and reveal no special additional risks to those already mentioned in other sections of the SPC. Preclinical effects were observed only at doses considered sufficiently in excess of the maximum human dose, thus being not relevant to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In the tablet core:

- Sucrose
- Gelatin (E441)
- Croscarmellose sodium (E468)
- Magnesium stearate (E470b)

In the filmcoating:

- Refined castor oil
- Saccharin sodium (E954)
- Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.
5 weeks after first opening.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

HDPE container with LDPE cap.

Pack sizes:
100, 200 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Fresenius Medical Care Nephrologica Deutschland GmbH
61346 Bad Homburg v.d.H.
Germany

8 MARKETING AUTHORISATION NUMBER

PA1350/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th February 2008.

10 DATE OF REVISION OF THE TEXT