SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Calcitriol 0.5 microgram Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 micrograms (mcg) of calcitriol.

Excipient(s) with known effect:
Each capsule contains 10.79 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.
Opaque, green, oblong, soft gelatine capsules imprinted 0.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Established post-menopausal osteoporosis.
Renal osteodystrophy in patients with chronic renal failure, in particular those undergoing haemodialysis. Secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (pre-dialysis). Hypoparathyroidism, whether idiopathic or post-surgical.
Pseudohypoparathyroidism.
Vitamin-D dependent rickets.
Vitamin-D resistant hypophosphataemic rickets.

4.2 Posology and method of administration

Posology
The dose of calcitriol capsules should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcaemia.
Treatment with calcitriol must always be started with the lowest possible dose and the dosage must not be increased without careful monitoring of serum calcium (see “Monitoring the patients”).

The effectiveness of treatment depends in part on an adequate daily intake of calcium, which should be augmented by dietary changes or supplements if necessary.

As calcitriol facilitates the absorption of calcium by the gastrointestinal tract, a lower calcium intake may be maintained in some patients under treatment with this medicinal product. Patients who are susceptible to hypercalcaemia may only require low doses of calcium and no supplementation.

Monitoring the patients
The necessary routine diagnostic tests include determining the serum calcium, phosphorus, magnesium and alkaline phosphatase levels, and the calcium and phosphate levels in the urine in the 24-hour test. During the stabilisation phase of the calcitriol treatment, the serum calcium must be checked at least twice a week. Once the optimum dose of calcitriol has been determined, the serum calcium need only be checked once a month (or as described below for the individual indications). The samples for evaluating the serum calcium must be taken without using a tourniquet.

Should the serum calcium levels rise to 1 mg/100ml (250 μmol/l) above normal (9 to 11 mg/100 ml or 2250 – 2750 μmol/l), or serum creatinine rises to > 120 μmol/l, treatment with calcitriol should be stopped immediately until normocalcaemia ensues.

The serum calcium and phosphate levels must be checked every day during the hypercalcaemia period. To facilitate rapid normalisation of the serum calcium levels, the calcium supplement, used in the treatment of renal osteodystrophy, hypoparathyroidism and rickets, may even be stopped.

Once the values have normalised, the calcitriol treatment may be resumed at a daily dose that is 0.25 mcg lower than the previous dose. The quantity of calcium taken in the daily diet must be estimated and, if indicated, the intake must be adjusted.

Adults

Renal Osteodystrophy (patients on haemodialysis)
The efficacy of the treatment is dependent on the simultaneous intake of calcium: adult patients must be given a calcium supplement of 600 1000 mg per day.
The initial recommended daily dose is 0.25 mcg of calcitriol. In patients with normal or only slightly reduced calcium levels, doses of 0.25 mcg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within 2 - 4 weeks, the daily dosage may be increased by 0.25 mcg at 2 - 4 week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to daily doses of between 0.5 mcg and 1.0 mcg. If hypercalcaemia is detected, the administration of calcitriol and the calcium supplement should be stopped immediately until the serum calcium normalizes. The treatment should then be resumed at a daily dose that is 0.25 mcg lower than the previous dose.
Higher doses may be necessary if barbiturates or anticonvulsants are administered at the same time.

An oral calcitriol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal doses given at the end of the dialysis has been shown to be

effective in patients with osteodystrophy refractory to continuous therapy. A maximum total cumulative dosage of 12 mcg per week should not be exceeded.

Post-menopausal Osteoporosis

The recommended dose of calcitriol is 0.25 mcg twice daily.
Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6 monthly intervals thereafter.

During the first month of treatment, the serum calcium should be checked at least once a week. In case of hypercalcaemia (>11.5 mg/100 ml), the administration of calcitriol should be stopped until the serum calcium normalizes. At the doctor's discretion, it may be combined with calcitonin (especially in the case of high-turnover osteoporosis).

Secondary hyperparathyroidism (pre-dialysis patients):
The recommended initial dose of calcitriol for treating secondary hyperparathyroidism and the consequential metabolic bone disease patients with moderate to severe renal failure, i.e. creatinine clearance (CCr) of between 15 and 55 ml/min., is 0.25 mcg/day in adults. If necessary the dose may be increased to 0.5 mcg/day.

Hypoparathyroidism and rickets
The recommended initial dose of calcitriol is 0.25 mcg per day, to be administered in the morning. If a satisfactory response is not obtained in the biochemical parameters and the clinical profile of the disease, the dose may be increased at intervals of 2-4 weeks. The serum calcium must be monitored at least twice a week during this period. In the case of hypercalcaemia, the administration of calcitriol must be stopped immediately until the serum calcium normalises. A reduction in the calcium intake through diet must also be carefully evaluated.
A malabsorption syndrome may sometimes be observed in patients with hyperparathyroidism: in these cases higher doses of calcitriol may be required.

Paediatric population
The safety and efficacy of calcitriol capsules in children have not been sufficiently investigated to enable dosing recommendations. Limited data are available for the use of calcitriol capsules in paediatric patients.

Elderly
Elderly patients do not require particular dosage adjustments. The general recommendations on monitoring calcium and creatinine serum levels must be followed.

Method of administration

Calcitriol capsules are for oral administration only. The capsules should be swallowed with little water.

4.3 Contraindications

Calcitriol is contraindicated:

- In all diseases associated with hypercalcemia
- In patients with evidence of metastatic calcification
- Hypersensitivity to the active substance (or to active substances belonging to the same class) or to any of the excipients listed in section 6.1
- If there is evidence of vitamin D toxicity

4.4 Special warnings and precautions for use

There is a close correlation between treatment with calcitriol and the development of hypercalcemia.

All other vitamin D compounds and their derivative, including proprietary compounds or foodstuffs which may be “fortified” with vitamin D, should be withheld during treatment with calcitriol.

An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia.

As soon as the serum calcium levels rise to 1 mg/100 ml (250 μmol/l) above normal (9-11 mg/100 ml, or 2250-2750 μmol/l), or serum creatinine rises to > 120 μmol/l, treatment with calcitriol should be stopped immediately until normocalcemia ensues (see section 4.2).

Immobilized patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcemia.

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphatemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate binding agents and low phosphate diet.

The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2.

Patients with vitamin D-resistant rickets (familial hypophosphatemia) who are being treated with calcitriol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by calcitriol should be taken into account since this effect may modify the need for phosphate supplementation.

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with calcitriol, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from a long acting vitamin D preparation (e.g. ergocalciferol (vitamin D_2) or colecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcaemia (see section 4.5).

Patients with normal renal function who are taking calcitriol should avoid dehydration. Adequate fluid intake should be maintained.

In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatinine.

In patients with postmenopausal osteoporosis, careful monitoring of renal function and blood calcium is essential before initiating therapy and at regular intervals during treatment with calcitriol (see section 4.2).

Excipient(s)

Sorbitol
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Sodium (component of Quinoline Yellow)
This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Since calcitriol is the most effective vitamin D metabolite, no other vitamin D preparations should be prescribed during treatment with calcitriol, thereby ensuring that the development of hypervitaminosis D is avoided. If the patient is switched from ergocalciferol (vitamin D_2) to calcitriol, it may take a several months for the ergocalciferol level in the blood to return to the baseline value.

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcemia in such patients may precipitate cardiac arrhythmias (see section 4.4).

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

Magnesium-containing drugs (e.g. antacids) may cause hypermagnesemia and should therefore not be taken during therapy with calcitriol by patients on chronic renal dialysis.

Since calcitriol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration (normal values: 2-5 mg/100 ml, or 0.65-1.62 mmol/l).

Patients with vitamin D-resistant rickets (familial hypophosphatemia) should continue their oral phosphate therapy. However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Administration of enzyme inducers such as phenytoin or phenobarbital may lead to increased metabolism and hence reduced serum concentrations of calcitriol. Therefore higher doses of calcitriol may be necessary if these drugs are administered simultaneously.

Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of calcitriol during pregnancy has not been established.

Supravalvular aortic stenosis has been produced in foetuses by near-fatal oral doses of vitamin D in pregnant rabbits. There is no evidence to suggest that vitamin D is teratogenic in humans even at very high doses. Calcitriol should be used during pregnancy only if the benefits outweigh the potential risk to the foetus.

Breast-feeding

It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcemia in the mother and for adverse reactions from calcitriol in nursing infants, mothers may breastfeed while taking calcitriol, provided that the serum calcium levels of the mother and infant are monitored.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities.

4.8 Undesirable effects

The adverse reactions listed below reflect the experience from investigational studies of calcitriol, and the post-marketing experience.

The most commonly reported adverse reaction was hypercalcaemia.

The ADRs listed in the table below are presented by system organ class and frequency categories, defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Summary of ADRs occurring in patients receiving calcitriol:

System Organ Class	**Frequency**			
	Very common	**Common**	**Uncommon**	**Not known**
Immune system disorders				Hypersensitivity, urticaria
Metabolism and nutrition disorders	Hypercalcaemia		Decreased appetite	Polydipsia, dehydration, weight decreased
Psychiatric disorders				Apathy, Psychiatric disturbances
Nervous system disorders		Headache		Muscular weakness, sensory disturbance, Somnolence
Cardiac Disorders				Cardiac arrhythmias
Gastrointestinal disorders		Abdominal pain, Nausea	Vomiting	Constipation, abdominal pain upper, Paralytic ileus
Skin and subcutaneous tissue disorders		Rash		Erythema, pruritus
Musculoskeletal and connective tissue disorders				Growth retardation
Renal and urinary disorders		Urinary tract infection		Polyuria, Nocturia
General disorders and administration site conditions				Calcinosis, pyrexia, thirst

System Organ Class	Frequency			
	Very common	**Common**	**Uncommon**	**Not known**
Investigations			Blood creatinine increased	

Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcemia) (see sections 4.2 and 4.4).

Occasional acute symptoms include decreased appetite, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalization of elevated serum calcium within a few days of treatment withdrawal, i.e. much faster than in treatment with vitamin D_3 preparations.

Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation and urinary tract infections.

For signs and symptoms of acute or chronic calcitriol intoxication, see section 4.9.

In concurrent hypercalcemia and hyperphosphatemia of > 6 mg/100 ml or > 1.9 mmol/l, calcinosis may occur; this can be seen radiographically.

Hypersensitivity reactions including rash, erythema, pruritus and urticaria may occur in susceptible individuals.

Laboratory Abnormalities
In patients with normal renal function, chronic hypercalcemia may be associated with blood creatinine increase. A few cases of abnormal increases in neutrophils and lymphopenia have been described.

Post-Marketing
The number of adverse effects reported from clinical use of calcitriol over a period of 15 years in all indications is very low with each individual effect, including hypercalcemia, occurring at a rate of 0.001 % or less.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with calcitriol may give rise to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2. A high calcium level in the dialysate may contribute to the development of hypercalcemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.

Chronic symptoms: dystrophy (weakness, loss of weight), sensory disturbances, possibly fever with thirst, polyuria, dehydration, apathy, arrested growth and urinary tract infections. Hypercalcemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

Treatment of asymptomatic hypercalcemia: (See section 4.2)

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote fecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Hypercalcemia at higher levels (> 3.2 mmol/l) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcaemia occur following prolonged treatment, calcitriol should be discontinued until plasma calcium levels have returned to normal. A low calcium diet will speed this reversal. Calcitriol can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent haemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues
ATC Code: A11C C04.

Mechanism of action
Calcitriol is the most active known form of vitamin D3 in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation. The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

The pharmacological effect of a single dose of calcitriol lasts about 3-5 days.

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to DNA sites to modify the expression of target genes.
The two known sites of action of calcitriol are the intestine and bones.
There appears to be a protein in the mucosa of the human intestine which binds to the calcitriol receptor.
Calcitriol is a synthetic preparation of calcitriol. Oral administration of calcitriol to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcaemia are improved, thereby reversing the signs and symptoms of bone disease.
In patients with severe renal failure, in particular those who have been undergoing periodical haemodialysis for some time, the formation of endogenous calcitriol gradually decreases and may even cease completely. The resulting hypocalcaemia and secondary hyperparathyroidism are the main causes of metabolic bone disease in renal failure, although other substances toxic to bone that accumulate in uraemia (for example aluminium) may contribute.

In patients with renal osteodystrophy, the oral administration of calcitriol normalises intestinal absorption of calcium, hypocalcaemia, elevated serum alkaline phosphatase levels and serum concentration of parathyroid hormone, apart from alleviating bone and muscle pain.

In patients with hypoparathyroidism, whether idiopathic or post-surgical, calcitriol alleviates hypocalcaemia and the clinical profile. In pseudohypoparathyroidism, it re-establishes normal intestinal absorption of calcium, corrects hypocalcaemia and reduces circulating levels of parathyroid hormone. In vitamin-D resistant hypophosphataemic rickets, the administration of calcitriol leads to an improvement in the clinical profile and normalisation of circulating phosphates.

In patients with post-menopausal osteoporosis, the oestrogen deficiency causes reduced endogenous synthesis of calcitriol, resulting in decreased intestinal absorption of calcium and bone mineralisation processes.
The administration of calcitriol increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of calcitriol are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

5.2 Pharmacokinetic properties

<u>Absorption</u>

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1 mcg. Calcitriol in healthy subjects were found within 3-6 hours.
Absorption is confirmed by a rapid increase in calcium in the urine, already verifiable seven hours after administration. A dose-correlated biological response is demonstrated by the increase in calcium excretion in the urine with doses of 0.5 and 1.0 mcg administered twice a day.

After a single oral dose of 0.5 mcg calcitriol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/ml to 60.0 ± 4.4 pg/ml after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/ml after 24 hours.

Distribution

During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated, and increased binding to lipoproteins and albumin occurs.

Biotransformation

Calcitriol is hydroxylated and oxidised in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.

Several metabolites with different degrees of vitamin D activity have been identified.

Elimination

The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts 3-5 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 µg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.
The steady state values, reached with doses of 0.5 mcg twice a day, decrease to baseline levels after the medicinal product has been stopped, with a half-life of about three and a half hours.

Special populations
Patients with hepatic impairment
The absorption of calcitriol may be delayed in patients with liver and biliary disease.
Patients with renal impairment
The elimination half-life of calcitriol is about twice as long in patients with chronic renal failure and patients on haemodialysis compared with healthy volunteers. In patients with nephritic syndrome, the T_{max} was 4 hours and the half-life 16.2 hours. Patients undergoing haemodialysis have a T_{max} for calcitriol of 8-12 hours with a half-life of 21.9 hours.

5.3 Preclinical safety data

The acute toxicity of calcitriol has been evaluated in mice and rats. After oral administration the LD50 in mice is 2 mg/kg, and in rats >5 mg/kg.

Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to 6 months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcaemia.

The chronic toxicity of calcitriol was evaluated in rats and dogs. The compound was administered per os to three groups of rats and dogs, for a duration of 26 weeks, at doses of 0.02, 0.08 and 0.30 mcg/kg/day. The groups of rats that received medium and high doses showed decreased body weight, reduced food consumption, increased serum calcium; these changes were absent or less marked in the group that received the lower doses. The dogs that received the high and medium doses presented marked anorexia, severe weight loss, deterioration in physical condition, increase in serum calcium, metastatic calcification of soft tissue and bone alterations. These findings were less marked in the dogs of the group that received 0.02 mcg/kg/day.

Reproductive toxicity studies in rats indicated that oral doses up to 300 ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, multiple foetal abnormalities were observed in two litters at an oral maternally toxic dose of 300 ng/kg/day and one litter at 80 ng/kg/day, but not at 20 ng/kg/day (twice the usual human dose). Although there were no statistically significant differences between treated groups and controls in the numbers of litters or foetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules contain:
Butylated hydroxyanisole (E320)
Butylated hydroxytoluene (E321)
Fractionated coconut oil.

Capsule shell contains:
Gelatin
Glycerol (E422)
Sorbitol (E420)
Titanium dioxide (E171)
Quinoline yellow (E104) (contains sodium)
Patent blue (E131)

The printing ink contains:

Shellac (E904) Glaze
Black iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Polypropylene tablet containers with LDPE caps in packs of 20, 30 and 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0942

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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