SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

QALYVIZ 0.25 mcg Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Calcitriol (obtained from sheep wool) 0.25 mcg

Excipients:
Sorbitol 14 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsules.
One half is brown-orange to red-orange colored, opaque; the other half is white colored, opaque soft capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

QALYVIZ is indicated for:

- Established postmenopausal osteoporosis.
- Renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis.
- Postsurgical hypoparathyroidism.
- Idiopathic hypoparathyroidism.
- Pseudohypoparathyroidism.
- Vitamin D-dependent rickets.
- Hypophosphatemic vitamin D-resistant rickets.
- Predialysis patients: QALYVIZ is indicated for the treatment of predialysis patients, i.e. for the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe chronic renal failure (Ccr 15 to 55 ml/min); in children, the creatinine clearance value must be corrected for a surface area of 1.73 square meters. A serum iPTH level of ≥100pg/ml is strongly suggestive of secondary hyperparathyroidism.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The optimal daily dose of QALYVIZ must be carefully determined for each patient on the basis of the serum calcium level. QALYVIZ therapy should always be started at the lowest possible dose and should not be increased without careful monitoring of serum calcium (see ‘‘Patient monitoring’’).

A prerequisite for optimal efficacy of QALYVIZ is adequate but not excessive calcium intake (in adults: approximately 800 mg daily) at the beginning of therapy. Calcium supplements may be necessary.

Because of improved calcium absorption from the gastrointestinal tract, some patients on QALYVIZ may be maintained on a lower calcium intake. Patients who tend to develop hypercalcemia may require only low doses of calcium or no supplementation at all. The total daily calcium intake (i.e. from food, and, where applicable, from medicines) should average approximately 800 mg and should not exceed 1000 mg.

Patient monitoring
During the stabilization phase of treatment with QALYVIZ, serum calcium levels should be checked at least twice weekly. When the optimal dosage of QALYVIZ has been determined, serum calcium levels should be checked every month (or as given below for individual indications). Samples for serum calcium estimation should be taken without a tourniquet.

As soon as the serum calcium levels rise to 1 mg/100 mL (250 micromole/L) above normal (9 to 11 mg/100 mL, or 2250-2750 micromole/L), or serum creatinine rises to > 120 micromole/L, treatment with QALYVIZ should be stopped immediately until normocalcemia ensues. During the periods of hypercalcemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, the treatment with QALYVIZ can be continued, at a daily dose 0.25 microgram lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated.

Postmenopausal osteoporosis
The recommended dosage for QALYVIZ is 0.25 microgram twice daily.
Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6-month intervals thereafter.

Renal osteodystrophy (dialysis patients)
The initial daily dose is 0.25 microgram. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25 microgram 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 microgram at two to four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5 microgram and 1.0 microgram daily.

An oral QALYVIZ pulse therapy with an initial dosage of 0.1 microgram/kg/week split into two or three equal dosages given at night was found to be effective even in patients refractory to continuous therapy. A maximum total cumulative dosage of 12 microgram per week should not be exceeded.

Secondary hyperparathyroidism (pre-dialysis patients)
The recommended initial dosage of QALYVIZ for the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe renal failure i.e. creatinine clearance (Ccr) 15 to 55 mL/min, in children corrected for a surface area of 1.73 m^2, the recommended initial dose is 0.25 microgram/day in adults and pediatric patients 3 years of age and older.. This dosage may be increased if necessary to 0.5 microgram/day. For pediatric patients less than 3 years of age, the recommended initial dosage of QALYVIZ is 10 to 15 ng/kg/day.

Hypoparathyroidism, rickets
The recommended initial dose of QALYVIZ is 0.25 microgram/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease is not observed, the dose may be increased at two to four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. If hypercalcemia is noted, QALYVIZ should be

immediately discontinued until normocalcemia ensues. Careful consideration should also be given to lowering the dietary calcium intake.

Malabsorption is occasionally noted in patients with hypoparathyroidism; hence, larger doses of QALYVIZ may be needed.

If the physician decides to prescribe QALYVIZ to a pregnant woman with hypoparathyroidism, an increased dose may be required during the latter half of gestation, with dose reduction postpartum or during lactation.

Method of administration
For oral administration. QALYVIZ capsules should be swallowed whole preferably with some water.

Additional information on special populations

Renal Impairment
Information on the use of QALYVIZ in patients with renal impairment is given above.

Hepatic Impairment
The safety and efficacy of QALYVIZ in patients with hepatic impairment have not been studied.

Pediatric population
The safety and efficacy of QALYVIZ in the pediatric population have not been studied.

Geriatric population
No specific dose adjustment is required in elderly patients. General recommendations for monitoring serum calcium and creatinine should be observed.

4.3 Contraindications
QALYVIZ is contraindicated:
- in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the excipients listed in section 6.1
- in all diseases associated with hypercalcemia
- in patients with evidence of metastatic calcification
- 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. 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 hypercalcemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognize the symptoms of hypercalcemia. As soon as the serum calcium levels rise to 1 mg/100 mL (250 micromole/L) above normal (9-11 mg/100 mL, or 2250-2750 micromole/L), or serum creatinine rises to > 120 micromole/L, treatment with QALYVIZ 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 QALYVIZ must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by QALYVIZ should be taken into account since this effect may modify the need for phosphate supplementation. The regular laboratory investigations that are required include serum determinations of calcium, phosphorus, magnesium and alkaline phosphatase and of the calcium and phosphate content in 24-hour urine. During the stabilization phase of treatment with QALYVIZ, serum calcium levels should be checked at least twice weekly (see section 4.2).

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with QALYVIZ, 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 several months for the ergocalciferol level in the blood to return to the baseline value (see section 4.9).

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

QALYVIZ contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 medicines (e.g. antacids) may cause hypermagnesemia and should therefore not be taken during therapy with QALYVIZ by patients on chronic renal dialysis.

Since QALYVIZ 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 absorption of phosphate by QALYVIZ should be taken into account since this effect may modify the need for phosphate supplementation.

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

4.6 Pregnancy and lactation

General recommendation:
Pregnancy category is C.

Women of child-bearing potential/Contraception
There are no adequate data on the use of vitamin D in pregnant women. Women of childbearing potential are advised to use effective contraception during treatment.

Pregnancy
Supravalvular aortic stenosis has been produced in fetuses 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. QALYVIZ should be used during pregnancy only if the benefits outweigh the potential risk to the fetus.

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

Fertility
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 fetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

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
Clinical Trials:
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 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).

<u>Immune System Disorders</u>
Not known: Hypersensitivity, urticaria

<u>Metabolism and Nutrition Disorders</u>
Very common: Hypercalcaemia

Uncommon: Decreased appetite

Not known: Polydipsia, dehydration

Nervous System Disorders
Common: Headache

Not known: Sensory disturbance, muscular weakness

Gastrointestinal Disorders
Common: Nausea, abdominal pain

Uncommon: Vomiting

Not known: Constipation, abdominal pain upper

Skin and subcutaneous tissue disorders
Common: Rash

Not known: Erythema, pruritus

Musculoskeletal and Connective Tissue Disorders
Not known: Growth retardation

Renal and Urinary Disorders
Common: Urinary tract infection

Not known: Polyuria

General disorders and administration site conditions
Not known: Calcinosis, pyrexia, thirst

Investigations
Uncommon: Blood creatinine increased

Not known: Weight decreased

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.

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 hypercalcaemia may be associated with a blood creatinine increased.

Postmarketing
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 authorization 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.

4.9 Overdose
Treatment of asymptomatic hypercalcemia (see section 4.2):
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 QALYVIZ 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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vitamin D and analogues
ATC code: A11CC04

Mechanism of action:
The two known sites of action of calcitriol are intestine and bone.

A calcitriol receptor-binding protein appears to exist in the mucosa of human intestine. Additional evidence suggests that calcitriol may also act on the kidney and the parathyroid glands. Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. In acutely uremic rats calcitriol has been shown to stimulate intestinal calcium absorption.

The kidneys of uremic patients cannot adequately synthesize calcitriol, the active hormone formed from precursor Vitamin D. Resultant hypocalcaemia and secondary hyperparathyroidism are a major cause of the metabolic bone disease of renal failure. However, other bone-toxic substances which accumulate in uremia (e.g., aluminum) may also contribute.

The beneficial effect of calcitriol in renal osteodystrophy appears to result from correction of hypocalcaemia and secondary hyperparathyroidism. It is uncertain whether calcitriol produces other independent beneficial effects.

Clinical trials/efficacy studies:
Calcitriol is one of the most important active metabolites of vitamin D3. It is normally formed in the kidney from its precursor, 25-hydroxycholecalciferol (25-HCC). Physiological daily production is normally 0.5-1.0 microgram and is somewhat higher during periods of increased bone synthesis (e.g. growth or pregnancy). Calcitriol promotes intestinal absorption of calcium and regulates bone mineralization. The pharmacological effect of a single dose of calcitriol lasts about 3-5 days.

The key role of calcitriol in the regulation of calcium homeostasis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basis for its therapeutic effects in osteoporosis.

In patients with marked renal impairment, synthesis of endogenous calcitriol is correspondingly limited or may even cease altogether. This deficiency plays a key role in the development of renal osteodystrophy.

In patients with renal osteodystrophy, oral administration of calcitriol normalizes reduced intestinal absorption of calcium, hypocalcaemia, increased serum alkaline phosphatase and serum parathyroid hormone concentration. It alleviates bone and muscle pain and corrects the histological alterations that occur in osteitis fibrosa and other mineralization defects.

In patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudohypo-parathyroidism, hypocalcaemia and its clinical manifestations are alleviated by calcitriol therapy.

In patients with vitamin D-dependent rickets, serum levels of calcitriol are low or absent. As the endogenous production of calcitriol in the kidney is insufficient, calcitriol is considered as a replacement therapy.

In patients with vitamin D-resistant rickets and hypophosphatemia in whom plasma calcitriol levels are reduced, treatment with calcitriol reduces tubular elimination of phosphates and, in conjunction with concurrent phosphate treatment, normalizes bone development.

Patients with various other forms of rickets, e.g. in association with neonatal hepatitis, biliary atresia, cystinosis and dietary calcium and vitamin D deficiency, have also benefited from calcitriol therapy.

5.2 Pharmacokinetic properties

General specifications

Absorption
Peak plasma concentrations following a single oral dose of 0.25-1.0 microgram calcitriol were reached within 2-6 hours.

Distribution
During transport in the blood, calcitriol and other vitamin D metabolites are bound to specific plasma proteins.

Metabolism
Calcitriol is hydroxylated and oxidized in the kidney and in the liver by a specific cytochrome P450 isoenzyme; 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. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range up to 165 μg single oral dose. The pharmacological effect of a single dose of calcitriol lasts at least 4 days. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

Characteristics in patients
Renal impairment:
In patients with nephrotic syndrome or in those undergoing hemodialysis, serum levels of calcitriol were reduced and time to peak levels was prolonged.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Butylhydroxyanisole
Butylhydroxytoluene
Medium-chain triglycerides
Gelatin (bovine gelatin)
Glycerol
Sorbitol
Purified water
Titanium dioxide
Iron oxide yellow
Iron oxide red

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 30°C. Protect from moisture.

6.5 Nature and contents of packaging
Opaque PVC/Aclar– Aluminum foil blister packaging
In blister packs containing 30 soft capsules with a package leaflet in a cardboard box

6.6. Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. PRODUCT OWNER

Saba İlaç San. ve Tic. A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece - ISTANBUL/TURKEY

Manufacturer
Deva Holding A.S.
Çerkezköy Organize Sanayi Bölgesi, Karaağaç Mah.

8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION OF THE TEXT

01/2025