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PRODUCT MONOGRAPH

PRODUCT NAME : Bonky injection 1.0 μg

ACTIVE INGREDIENT : Calcitriol 1.0 μg

DOSAGE FORM : Injection

DESCRIPTION : Colorless to light yellow transparent solution in a brown glass ampoule.

INDICATIONS

1. Management of hypocalcemia in patients undergoing chronic renal dialysis.
2. Improvement of renal osteodystrophy through a significant reduction in elevated parathyroid hormone levels.

DOSAGE AND ADMINISTRATION

The appropriate dosage of this drug should be carefully determined for each individual patient.

Recommended Initial Dosage
The recommended initial dose is 0.5 μg of calcitriol three times weekly, corresponding to approximately 0.01 μg/kg body weight, administered every other day.
This drug may be administered as an intravenous bolus through the catheter at the end of hemodialysis.
If a satisfactory response in biochemical parameters and clinical symptoms is not observed, the dose may be increased by 0.25 ~ 0.50 μg at intervals of 2 ~ 4 weeks.
Most patients undergoing hemodialysis respond to doses ranging from 0.5 to 3.0 μg three times weekly, corresponding to approximately 0.01 ~ 0.05 μg/kg body weight.

Dosage-Related Precautions
1) Monitoring of serum calcium and phosphorus

Serum calcium and phosphorus levels must be measured at least twice a week during the period used to determine the appropriate dosage. However, if the serum calcium level exceeds the upper limit of the reference range by 0.5 mg/dL, the frequency of measurement should be increased (to at least once a week), and the drug should be administered with caution, considering a reduction in dosage. Furthermore, if the serum calcium level exceeds the upper limit of the reference range by 1 mg/dL, discontinue the medication immediately. After confirming that serum calcium levels have returned to within the normal range following the treatment interruption, resume administration while considering a dose reduction based on the pre-interruption dosage. In cases of hypoalbuminemia (serum albumin level < 4.0 g/dL), it is recommended to use the corrected value as a guide.

- Method for Calculating Corrected Calcium Levels:
  Corrected calcium level (mg/dL) = Serum calcium level (mg/dL) - Serum albumin level (g/dL) + 4.0

2) Ultimately, it is advisable to reduce the drug dosage in accordance with the decrease in parathyroid hormone (PTH) levels in response to treatment (as hypercalcemia is likely to develop if PTH levels are reduced excessively). The recommended dosage adjustment method is as follows.

Change in PTH Level	Dose Adjustment
No change or slight increase	Increase the dose
Less than 30% decrease	Increase the dose
More than 30% but less than 60% decrease	Maintain the current dose
More than 60% decrease	Reduce the dose
PTH level at 1.5–3 times the upper limit of normal	Maintain the current dose

WARNINGS AND PRECAUTIONS

1. Serious Warning

When opening an ampoule, glass fragments may enter the solution and cause adverse effects.
The ampoule should therefore be opened carefully to minimize contamination by glass fragments. Particular caution is required when the product is used in children or elderly patients.

2. Contraindications

This drug is contraindicated in the following patients:

1. Patients with hypersensitivity to this drug (vitamin D or its derivatives and analogs) or to any of its ingredients
2. Patients with hypercalcemia or signs of vitamin D toxicity.

3. Patients Requiring Special Caution

This drug should be administered with caution to:

- Pregnant women
- Breast-feeding women

ADVERSE REACTIONS

1. Hypersensitivity Reactions

Rare cases of hypersensitivity reactions, including anaphylaxis, localized redness at the injection site, and mild injection-site pain, have been reported.

2. Vitamin D Intoxication

Adverse reactions associated with this drug are generally similar to those observed following excessive intake of vitamin D.
Symptoms of vitamin D intoxication associated with hypercalcemia are classified by organ system as follows:

2.1 Gastrointestinal disorders

Polydipsia, Nausea, Vomiting, Dry mouth, Constipation ,Metallic taste ,Loss of appetite, Pancreatitis, Abdominal cramps

2.2 Psychiatric and nervous system disorders

Headache, Somnolence, Insomnia, Numbness of the hands, Dizziness, Confusion, Vertigo, Worsening of depression, Agitation, Anxiety, Rarely, overt psychosis

2.3 Cardiovascular disorders

Hypertension, Cardiac arrhythmia, Palpitations, Prolongation of the QT interval, Atrioventricular block, Atrial fibrillation

2.4 Musculoskeletal disorders

Bone pain, Arthralgia

2.5 Respiratory disorders

Rhinorrhea

2.6 Hepatobiliary and laboratory abnormalities

Increased AST, Increased ALT, Increased LDH, Increased gamma-glutamyl transpeptidase (GGT)

2.7 Renal disorders

Increased blood urea nitrogen (BUN)

2.8 Skin disorders

Pruritus, Acne

2.9 Eye disorders

Conjunctivitis associated with calcification, Photophobia, Conjunctival hyperemia

2.10 Other adverse reactions

Weakness, Myalgia, Pain in the extremities, Polyuria, Nocturia, Weight loss, High fever, Decreased libido, Proteinuria, Hypercholesterolemia, Metastatic calcification, Increased serum phosphorus, Increased serum calcium, Discomfort in the extremities, lumbar region, or anal region, Muscle weakness, Facial flushing, Dysphoria, Back pain, Chest tightness, Eosinophilia, Decreased or increased lymphocyte count, Increased hematocrit, Neutrophilia, Monocytosis, Thrombocytopenia, Increased hemoglobin, Increased hepatic transaminase levels, Increased alkaline phosphatase, Hypercalciuria, Hypermagnesemia, Hyperphosphatemia

3. Complications of Chronic Hypercalcemia

Chronic hypercalcemia may cause generalized vascular calcification, nephrocalcinosis, and calcification of other soft tissues.

GENERAL PRECAUTIONS

1) The therapeutic effect of this drug is based on the assumption that the patient receives an adequate daily calcium intake. The recommended daily calcium intake for adults is 800 mg. To ensure adequate daily calcium intake, the physician should prescribe calcium supplements or provide the patient with appropriate dietary instructions. Because this drug improves gastrointestinal absorption of calcium, some patients may be maintained on a reduced calcium intake or without calcium supplementation.

2) Overdosage of this drug may cause hypercalcemia and, rarely, hypercalciuria. During initial dose adjustment, serum calcium and phosphorus levels should be measured at least twice weekly. If hypercalcemia occurs, treatment should be discontinued immediately. Treatment may be resumed after confirming that serum calcium has returned to the normal range. Dose reduction should be considered based on the previously administered dose. Progressive hypercalcemia caused by excessive doses of vitamin D or its metabolites may be sufficiently serious to require emergency treatment.

3) In dialysis patients, non-aluminum-containing phosphate binders should be used to control serum phosphorus levels.

4) A low-calcium dialysate may be effective in patients who develop hypercalcemia.

5) The serum calcium-phosphorus product, Ca × P, should not exceed 70 $(mg/dL)^2$.

6) Patients and their families should be informed that strict adherence to instructions regarding dosage, diet, and calcium supplementation is essential. Patients should be instructed not to use non-prescription medicines without consulting a healthcare professional, particularly antacids containing magnesium. Patients should also be instructed on how to recognize the symptoms of hypercalcemia and to follow the recommended precautions if such symptoms occur.

7) **Essential laboratory monitoring**

Serum concentrations of calcium, phosphorus, magnesium, and alkaline phosphatase should be measured periodically. Calcium and phosphorus levels in 24-hour urine should also be measured. During the initial treatment period, serum calcium and phosphorus should be measured frequently, at least twice weekly. Abnormally low PTH levels may result in adynamic bone disease. Development of adynamic bone disease may be monitored by bone biopsy or measurement of

PTH levels. When bone biopsy is indicated for another diagnostic reason, it may also be used to monitor the development of adynamic bone disease. In other circumstances, measurement of PTH levels may be used instead of bone biopsy. If the PTH level in a patient receiving this drug falls below the recommended target range of 1.5–3 times the upper limit of normal, the dose should be reduced or treatment should be discontinued. As abrupt discontinuation may cause a rebound effect, gradual dose reduction to an appropriate maintenance dose is recommended. Periodic ophthalmologic examinations or radiographic examinations of suspected anatomical sites may be indicated for the early detection of metastatic calcification.

8) Bone loss may be excessive immediately after transplantation and may exceed 5% per year. The efficacy of this drug in the treatment of post-transplant bone loss has not been established. Therefore, it should not be used for this indication.

9) The efficacy of this drug in patients with osteoporosis caused by postmenopausal estrogen deficiency has not been established. Therefore, it should not be used for this indication.

DRUG INTERACTIONS

1) This drug is one of the most potent active metabolites of vitamin D. Concomitant administration of vitamin D or other vitamin D metabolites should therefore be discontinued during treatment with this drug.

2) This drug should not be administered concomitantly with magnesium-containing antacids because such combination may cause hypermagnesemia.

3) The dose should be carefully determined in patients receiving digitalis or other cardiac glycosides because hypercalcemia may precipitate cardiac arrhythmias.

4) The effects of vitamin D may be reduced in patients receiving barbiturates or anticonvulsants, particularly phenytoin.

5) Corticosteroids may antagonize the effects of vitamin D derivatives.

6) Concomitant administration with calcium preparations or thiazide diuretics may cause hypercalcemia.

USE IN SPECIAL POPULATIONS

1) Pregnancy

Oral administration of this drug to rabbits at doses 4–15 times the clinical dose resulted in teratogenic effects.
All 15 fetuses from three dams exhibited external and skeletal abnormalities. However, no increase in abnormalities compared with the control group was observed among 156 fetuses from another 23 dams.
The safety and efficacy of this drug in pregnant women have not been established.
This drug should be used during pregnancy only when the potential therapeutic benefit justifies the potential risk to the fetus.

2) Breast-feeding

It is not known whether this drug is excreted in human milk.
Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-fed infants, administration during breast-feeding should be avoided.
When treatment is considered essential, breast-feeding should be discontinued.

3) Pediatrics

The safety and efficacy of this drug in pediatric patients have not been established.

4) Geriatrics

Physiological functions are generally reduced in elderly patients. Therefore, the dose should be selected cautiously.
Treatment should generally be initiated at the lower end of the usual dosage range, with frequent consideration of decreased hepatic, renal, or cardiac function, concomitant diseases, and other drug therapies.

OVERDOSAGE

Overdosage of this drug may cause hypercalcemia, hypercalciuria, and hyperphosphatemia.
Concomitant administration of this drug with large amounts of calcium or phosphate may produce similar abnormalities.

1) Management of hypercalcemia and overdosage in dialysis patients

For hypercalcemia, defined as an increase in serum calcium of at least 1 mg/dL or 0.25 mmol/L above the upper limit of normal, treatment should be discontinued immediately.
A low-calcium diet should be initiated, and calcium supplementation should be discontinued.
Serum calcium levels should be measured daily until they return to normal.
Hypercalcemia generally resolves within 2–7 days.
When serum calcium has returned to the normal range, treatment may be resumed at a dose 0.5 μg lower than the previous dose.
Serum calcium should be measured at least twice weekly following each dose adjustment.
Persistent or markedly elevated serum calcium levels may be controlled by dialysis using a calcium-free dialysate.

2) Management of accidental acute overdosage

Treatment of accidental acute overdosage should consist of general supportive measures.
Because of the risk of hypercalcemia, serial measurement of serum electrolytes, particularly calcium, urinary calcium excretion, and electrocardiographic assessment should be performed.
These assessments are essential in patients receiving digitalis.
Calcium supplementation should be discontinued, and a low-calcium diet should be initiated.
Because the pharmacological action of this drug is relatively short, generally 3–5 days, additional treatment may not be required.
However, when serum calcium remains persistently or markedly elevated, various therapeutic measures may be considered depending on the patient's condition.
Reported measures include Intravenous fluid administration, Forced diuresis with saline, Peritoneal dialysis or hemodialysis using a calcium-free dialysate, Bisphosphonates, Mithramycin, Calcitonin, Corticosteroids, Gallium nitrate.

ADMINISTRATION PRECAUTIONS

1) Inspect the solution for particulate matter and discoloration before administration.
2) Do not mix this drug with other medicinal products during administration.
3) Use promptly after opening and discard any unused portion.
4) Administer by slow intravenous injection over approximately 30 seconds.

STORAGE AND HANDLING

1) Keep out of reach of children.
2) Store at room temperature between 15°C and 25°C. Protect from excessive heat and direct sunlight. Do not freeze.
3) Keep the product in its original container and ensure that the container is tightly closed. Transferring the drug to another container may result in medication errors or deterioration of product quality.

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OTHERS

1. Carcinogenicity, mutagenicity, and impairment of fertility

1) The carcinogenic potential of this drug has not been evaluated in long-term animal studies.
2) No evidence of mutagenicity was observed in an in vitro Ames test. However, genotoxicity was observed in an in vivo mouse micronucleus test following oral administration of this drug.
3) Oral administration of this drug had no significant effect on reproductive capacity.

2. A 12-week, randomized, double-blind, placebo-controlled clinical trial evaluated the safety and efficacy of this drug in 35 pediatric patients aged 13–18 years with end-stage renal disease undergoing hemodialysis. Of the enrolled patients, 66% were male and 57% were Black American. All patients had received some form of vitamin D therapy before entering the study. The initial doses were 0.5 μg, 1.0 μg, or 1.5 μg three times weekly, according to baseline intact parathyroid hormone levels of: Below 500 pg/mL, 500–1,000 pg/mL, Above 1,000 pg/mL. The dose was subsequently adjusted in increments of 0.25 μg according to serum intact PTH, calcium, and Ca × P levels. The mean baseline intact PTH level was 769 pg/mL in 16 patients treated with this drug and 897 pg/mL in 19 patients receiving placebo. The mean weekly dose of this drug ranged from 0.1 to 1.4 μg. The primary efficacy endpoint was defined as two consecutive reductions of at least 30% from baseline in intact PTH. This endpoint was achieved in 44% of patients treated with this drug compared with 16% of patients receiving placebo. One patient treated with this drug experienced transient hypercalcemia, defined as a serum calcium level above 11.0 mg/dL. A Ca × P value above 75 was observed in 38% of patients treated with this drug and in 11% of patients receiving placebo.

Storage Store : below 30°C.

Shelf life : 36 months.

Packaging : 10 Ampoules / Box

Manufacturer : Aju Pharma Co. Ltd.