For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

GEMITROL KIT

1. Generic Name

Combipack of Calcitriol, Calcium Carbonate & Zinc Capsules and Risedronate Sodium Tablet U.S.P.

2. Qualitative and quantitative composition

A. Risedronate Sodium Tablet I.P.:

1 Tablet

Each film-coated tablet contains:

Risedronate Sodium I.P. 35 mg

(As Risedronate Sodium Hemi-Pentahydrate)

Colours: Sunset Yellow FCF & Titanium Dioxide I.P.

B. FDC of Calcitriol+ Calcium Carbonate +Zinc:

6 Capsules

Each soft gelatin capsule contains:

Calcitriol I.P……. 0.25 mcg

Calcium Carbonate I.P…….500 mg

(Equivalent to elemental Calcium 200 mg)

Zinc (as Zinc Sulphate Monohydrate I.P.) …..7.5 mg

Excipients…….q.s.

Approved colours used in capsule shells.

Appropriate overage of Vitamin is added to compensate loss on storage.

The Excipients Are Glycerin, Sorbitol, Methyl Paraben Sodium, Propyl Paraben Sodium, Ferric Oxide, Black, Colloidal Silicon Dioxide, Butylated Hydroxy Anisole, Butylated Hydroxy Toluene, Lecithin, Yellow Beeswax, Medium-Chain Triglycerides, Titanium Dioxide, Glycerin, Light Liquid Paraffin, Soyabean Oil.

3. Dosage form and strength

Tablet-35 mg

Capsules-0.25 mcg+200 mg+7.5 mg

4. Clinical particulars

4.1 Therapeutic indication

Gemitrol kit is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

4.2 Posology and method of administration

The tablet containing Risedronate has to be taken one time on day-1, on an empty stomach; one soft gelatin capsule containing calcitriol, calcium carbonate, and zinc sulphate has to be taken every day in the morning after food from day 2 to day 7. If you forget to take the tablet on day-1, you can take it as recommended above on the next day morning. However, you must observe all the guidelines mentioned for taking the drug (as mentioned for day-1.) "You can start the therapy on any day of the week by consuming the capsule/tablet as specified on the strip for that particular day."

Method of administration

To be taken orally with water

Do not take two tablets on any day

4.3 Contraindications

- in all diseases associated with hypercalcaemia
- in patients with evidence of metastatic calcification
- in patients with known hypersensitivity to mentioned ingredients and (or drugs of the same class) and any of the constituent excipients. Angioedema, generalized rash, bullous skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported
- If there is evidence of vitamin D toxicity**.**
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes

4.4 Special warnings and precautions

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia. All other vitamin D compounds and their derivatives, 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 because 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 should be stopped immediately until normocalcaemia ensues. Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, 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 * phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2.

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.

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 hypercalcaemia may be associated with an increase in serum creatinine.

Calcitriol capsules contain sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Calcitriol capsules.

Drug Products with the Same Active Ingredient

Upper Gastrointestinal Adverse Reactions

Risedronate like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Risedronate is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers). Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue Risedronate and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6 to 8 ounces) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient. In patients who cannot comply with dosing instructions due to mental disability, therapy with Risedronate should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

Mineral Metabolism

Hypocalcemia has been reported in patients taking Risedronate. Treat hypocalcemia and other disturbances of bone and mineral metabolism before starting Risedronate therapy. Instruct patients to take supplemental calcium and vitamin D if their dietary intake is inadequate. Adequate intake of calcium and vitamin D is important in all patients, especially in patients with Paget's disease in whom bone turnover is significantly elevated.

Jaw Osteonecrosis

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including Risedronate. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (for example, tooth extraction, dental implants, and boney surgery), diagnosis of cancer, concomitant therapies (for example, chemotherapy,

corticosteroids, and angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (for example, periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). The risk of ONJ may increase with duration of exposure to bisphosphonates.

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment

Musculoskeletal Pain

In postmarketing experience, there have been reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are traverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (for example, prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Renal Impairment

Risedronate is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

Glucocorticoid-Induced Osteoporosis

Before initiating Risedronate for the treatment and prevention of glucocorticoid-induced osteoporosis, the sex steroid hormonal status of both men and women should be ascertained and appropriate replacement considered.

Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Risedronate have not been performed.

Excessive intake of zinc may lead to overdosage symptoms like nausea, severe vomiting, dehydration, restlessness and sideroblastic anaemia (secondary to zinc induced copper depletion). This kit should be avoided in patients on digitalis because hypercalcaemia in such patients may precipitate cardiac arrhythmias.

4.5 Drugs interactions

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 hypercalcaemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias.

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

Calcium Supplements/Antacids

Co-administration of Risedronate and calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of Risedronate.

Hormone Replacement Therapy

One study of about 500 early postmenopausal women has been conducted to date in which treatment with Risedronate 5 mg daily and estrogen replacement therapy was compared to estrogen replacement therapy alone. Exposure to study drugs was approximately 12 to 18 months and the primary endpoint was change in BMD. If considered appropriate, Risedronate may be used concomitantly with hormone replacement therapy.

Aspirin/Nonsteroidal Anti-Inflammatory Drugs

Of over 5700 patients enrolled in the Risedronate Phase 3 osteoporosis studies, aspirin use was reported by 31% of patients, 24% of whom were regular users (3 or more days per week). Forty-eight percent of patients reported NSAID use, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in placebo-treated patients (24.8%) was similar to that in Risedronate-treated patients (24.5%).

H2 Blockers and Proton Pump Inhibitors (PPIs)

Of over 5700 patients enrolled in the Risedronate Phase 3 osteoporosis studies, 21% used H2 blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the placebo-treated patients was similar to that in Risedronate-treated patients.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.) Calcitriol

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. It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcaemia 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.

Risedronate

Pregnancy Category C: There are no adequate and well-controlled studies of in pregnant women. Risedronate should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Bisphosphonates are incorporated into the bone matrix; from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.

In animal studies, pregnant rats received Risedronate during organogenesis at doses 1 to 26 times the human dose of 30 mg/day. Survival of neonates was decreased in rats treated during gestation with oral doses approximately 5 times the human dose and body weight was decreased in neonates from dams treated with approximately 26 times the human dose. The number of fetuses exhibiting incomplete ossification of sternebrae or skull from dams treated with approximately 2.5 times the human dose was significantly increased compared to controls. Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses approximately 5 times the human dose. A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses approximately equal to the human dose. The relevance of this finding to human use of Risedronate is unclear.

No significant fetal ossification effects were seen in rabbits treated with oral doses approximately 7 times the human dose (the highest dose tested). However, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.

Similar to other bisphosphonates, treatment during mating and gestation with doses of Risedronate sodium approximately the same as the 30 mg/day human dose resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (mg/m2). Actual animal doses were 3.2, 7.1 and 16 mg/kg/day in the rat and 10 mg/kg/day in the rabbit.

Nursing Mothers

Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. It is not known whether Risedronate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Risedronate, a decision should

be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Risedronate is not indicated for use in pediatric patients.

In the reported data the safety and effectiveness of Risedronate was assessed in a one-year, randomized, double blind, placebo-controlled study of 143 pediatric patients (94 received Risedronate) with osteogenesis imperfecta (OI). The enrolled population was predominantly patients with mild osteogenesis imperfecta (85% Type-I), aged 4 to less than 16 years, 50% male and 82% Caucasian, with a mean lumbar spine BMD Z-score of -2.08 (2.08 standard deviations below the mean for age-matched controls). Patients received either a 2.5 mg (less than or equal to 30 kg body weight) or 5 mg (greater than 30 kg body weight) daily oral dose. After one year, an increase in lumbar spine BMD in the Risedronate group compared to the placebo group was observed. However, treatment with Risedronate did not result in a reduction in the risk of fracture in pediatric patients with osteogenesis imperfecta. In Risedronate -treated subjects, no mineralization defects were noted in paired bone biopsy specimens obtained at baseline and month 12.

The overall safety profile of Risedronate in OI patients treated for up to 12 months was generally similar to that of adults with osteoporosis. However, there was an increased incidence of vomiting compared to placebo. In this study, vomiting was observed in 15% of children treated with Risedronate and 6% of patients treated with placebo. Other adverse events reported in greater than or equal to 10% of patients treated with Risedronate and with a higher frequency than placebo were: pain in the extremity (21% with Risedronate versus 16% with placebo), headache (20% versus 8%), back pain (17% versus 10%), pain (15% versus 10%), upper abdominal pain (11% versus 8%), and bone pain (10% versus 4%).

Geriatric Use

Of the patients receiving Risedronate in postmenopausal osteoporosis studies. 47% were between 65 and 75 years of age, and 17% were over 75. The corresponding proportions were 26% and 11% in glucocorticoid-induced osteoporosis trials, and 40% and 26% in Paget's disease trials. No overall differences in efficacy between geriatric and younger patients were observed in these studies. In the male osteoporosis trial, 28% of patients receiving Risedronate were between 65 and 75 years of age and 9% were over 75. The lumbar spine BMD response for Risedronate compared to placebo was 5.6% for subjects less than 65 years and 2.9% for subjects greater than or equal to 65 years. No overall differences in safety between geriatric and younger patients were observed in the Risedronate trials, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Risedronate is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min.

Hepatic Impairment

No studies have been performed to assess Risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

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. Though ask your doctor before handling any machines.

4.8 Undesirable effects

Calcitriol

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

The most commonly reported adverse reaction was hypercalcaemia.

The ADRs listed in below Table 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	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

System Organ Class	Very common	Common	Uncommon	Not known
General disorders and administration site conditions				Calcinosis, Pyrexia, Thirst
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. hypercalcaemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcaemia). 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 normalisation 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 hypercalcaemia and hyperphosphataemia 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 increase.

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 hypercalcaemia, occurring at a rate of 0.001 % or less.

Risedronate

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Postmenopausal Osteoporosis

Daily Dosing

The safety of Risedronate 5 mg once daily in the treatment of postmenopausal osteoporosis was assessed in four randomized, double blind, placebo-controlled multinational trials of 3232 women aged 38 to 85 years with postmenopausal osteoporosis. The duration of the trials was up to three years, with 1619 patients exposed to placebo and 1613 patients exposed to Risedronate 5 mg. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H2 antagonists were

included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 international units per day if their 25-hydroxyvitamin D3 level was below normal at baseline.

The incidence of all-cause mortality was 2.0% in the placebo group and 1.7% in the Risedronate 5 mg daily group. The incidence of serious adverse events was 24.6% in the placebo group and 27.2% in the Risedronate 5 mg group. The percentage of patients who withdrew from the study due to adverse events was 15.6% in the placebo group and 14.8% in the Risedronate 5 mg group. The most common adverse reactions reported in greater than 10 percent of subjects were: back pain, arthralgia, abdominal pain and dyspepsia. lists adverse events from the Phase 3 postmenopausal osteoporosis trials reported in greater than or equal to 5% of patients. Adverse events are shown without attribution of causality.

Adverse Events Occurring at a Frequency greater than or equal to 5% in Either Treatment Group Combined Phase 3 Postmenopausal Osteoporosis Treatment Trials		
	Placebo N = 1619	**5 mg** Risedronate **N = 1613**
Body System	**%**	**%**
Body as a Whole		
Infection	29.9	31.1
Back Pain	26.1	28.0
Accidental Injury	16.8	16.9
Pain	14.0	14.1
Abdominal Pain	9.9	12.2
Flu Syndrome	11.6	10.5
Headache	10.8	9.9
Asthenia	4.5	5.4
Neck Pain	4.7	5.4
Chest Pain	5.1	5.0
Allergic Reaction Cardiovascular System	5.9	3.8
Hypertension Digestive System	9.8	10.5
Constipation	12.6	12.9
Diarrhea	10.0	10.8
Dyspepsia	10.6	10.8
Nausea Metabolic & Nutritional Disorders	11.2	10.5
Peripheral Edema Musculoskeletal System	8.8	7.7
Arthralgia	22.1	23.7
Arthritis	10.1	9.6
Traumatic Bone Fracture	12.3	9.3
Joint Disorder	5.3	7.0
Myalgia	6.2	6.7
Bone Pain Nervous System	4.8	5.3
Dizziness	5.7	7.1
Depression	6.1	6.8
Insomnia Respiratory System	4.6	5.0
Bronchitis	10.4	10.0
Sinusitis	9.1	8.7
Rhinitis	5.1	6.2

Adverse Events Occurring at a Frequency greater than or equal to 5% in Either Treatment Group Combined Phase 3 Postmenopausal Osteoporosis Treatment Trials		
	Placebo N = 1619	**5 mg** Risedronate **N = 1613**
Body System	**%**	**%**
Pharyngitis	5.0	6.0
Increased Cough Skin and Appendages	6.3	5.9
Rash Special Senses	7.1	7.9
Cataract Urogenital System	5.7	6.5
Urinary Tract Infection	10.4	11.1

Gastrointestinal Adverse Events: The incidence of adverse events in the placebo and Risedronate 5 mg daily groups were abdominal pain (9.9% versus 12.2%), diarrhea (10.0% versus 10.8%), dyspepsia (10.6% versus 10.8%), and gastritis (2.3% versus 2.7%). Duodenitis and glossitis have been reported uncommonly in the Risedronate 5 mg daily group (0.1% to 1%). In patients with active upper gastrointestinal disease at baseline, the incidence of upper gastrointestinal adverse events was similar between the placebo and Risedronate 5 mg daily groups.

Musculoskeletal Adverse Events: The incidence of adverse events in the placebo and Risedronate 5 mg daily groups were: back pain (26.1% versus 28.0%), arthralgia (22.1% versus 23.7%), myalgia (6.2% versus 6.7%), and bone pain (4.8% versus 5.3%).

Laboratory Test Findings: in the reported data throughout the Phase 3 studies, transient decreases from baseline in serum calcium (less than 1%) and serum phosphate (less than 3%) and compensatory increases in serum PTH levels (less than 30%) were observed within 6 months in patients in osteoporosis clinical trials treated with Risedronate 5 mg once daily. There were no significant differences in serum calcium, phosphate, or PTH levels between placebo and Risedronate 5 mg once daily at 3 years. Serum calcium levels below 8 mg/dL were observed in 18 patients, 9 (0.5%) in each treatment arm (placebo and Risedronate 5 mg once daily). Serum phosphorus levels below 2 mg/dL were observed in 14 patients, 3 (0.2%) treated with placebo and 11 (0.6%) treated with Risedronate 5 mg once daily. There have been rare reports (less than 0.1%) of abnormal liver function tests.

Endoscopic Findings: In the Risedronate clinical trials, endoscopic evaluation was encouraged in any patient with moderate-to-severe gastrointestinal complaints, while maintaining the blind. Endoscopies were performed on equal numbers of patients between the placebo and treated groups [75 (14.5%) placebo; 75 (11.9%) Risedronate]. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% Risedronate).

Once-a-Week Dosing

The safety of Risedronate 35 mg once-a-week in the treatment of postmenopausal osteoporosis was assessed in a 1-year, double-blind, multicenter study comparing Risedronate 5 mg daily and Risedronate 35 mg once-a-week in postmenopausal women aged 50 to 95 years. The duration of the trials was one year, with 480 patients exposed to Risedronate 5 mg daily and 485 exposed to Risedronate 35 mg once a week. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H2 antagonists were included in these clinical trials. All women received 1000 mg of

elemental calcium plus vitamin D supplementation up to 500 international units per day if their 25hydroxyvitamin D3 level was below normal at baseline.

The incidence of all-cause mortality was 0.4% in the Risedronate 5 mg daily group and 1.0% in the Risedronate 35 mg once-a-week group. The incidence of serious adverse events was 7.1% in the Risedronate 5 mg daily group and 8.2% in the Risedronate 35 mg once-a-week group. The percentage of patients who withdrew from the study due to adverse events was 11.9% in the Risedronate 5 mg daily group and 11.5% in the Risedronate 35 mg once-a-week group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Gastrointestinal Adverse Events: The incidence of gastrointestinal adverse events was similar between the Risedronate 5 mg daily group and the Risedronate 35 mg once-a-week group: dyspepsia (6.9% versus 7.6%), diarrhea (6.3% versus 4.9%), and abdominal pain (7.3% versus 7.6%).

Musculoskeletal Adverse Events: Arthralgia was reported in 11.5% of patients in the Risedronate 5 mg daily group and 14.2% of patients in the Risedronate 35 mg once-a-week group. Myalgia was reported by 4.6% of patients in the Risedronate 5 mg daily group and 6.2% of patients in the Risedronate 35 mg once-a-week group.

Laboratory Test Findings: The mean percent changes from baseline at 12 months were similar between the Risedronate 5 mg daily and Risedronate 35 mg once-a-week groups, respectively, for serum calcium (0.4% versus 0.7%), phosphate (-3.8% versus -2.6%) and PTH (6.4% versus 4.2%).

Monthly Dosing

Two Consecutive Days per Month

The safety of Risedronate 75 mg administered on two consecutive days per month for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicenter study in postmenopausal women aged 50 to 86 years. The duration of the trial was two years; 613 patients were exposed to Risedronate 5 mg daily and 616 were exposed to Risedronate 75 mg two consecutive days per month. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H2 antagonists were included in this clinical trial. All women received 1000 mg of elemental calcium plus 400 to 800 international units of vitamin D supplementation per day.

The incidence of all-cause mortality was 1.0% for the Risedronate 5 mg daily group and 0.5% for the Risedronate 75 mg two consecutive days per month group. The incidence of serious adverse events was 10.8% in the Risedronate 5 mg daily group and 14.4% in the Risedronate 75 mg two consecutive days per month group. The percentage of patients who withdrew from treatment due to adverse events was 14.2% in the Risedronate 5 mg daily group and 13.0% in the Risedronate 75 mg two consecutive days per month group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 3.6% of patients on Risedronate 5 mg daily and 7.6% of patients on Risedronate 75 mg two consecutive days per month. These incidence rates are based on reporting of any of 33 acute phase reaction-like symptoms within 5 days of the first dose. Fever or influenza-like illness with onset within the same period were reported by 0.0% of patients on Risedronate 5 mg daily and 0.6% of patients on Risedronate 75 mg two consecutive days per month.

Gastrointestinal Adverse Events: The Risedronate 75 mg two consecutive days per month group resulted in a higher incidence of discontinuation due to vomiting (1.0% versus 0.2%)

and diarrhea (1.0% versus 0.3%) compared to the Risedronate 5 mg daily group. Most of these events occurred within a few days of dosing.

Ocular Adverse Events: None of the patients treated with Risedronate 75 mg two consecutive days per month reported ocular inflammation such as uveitis, scleritis, or iritis; 1 patient treated with Risedronate 5 mg daily reported uveitis.

Laboratory Test Findings: When Risedronate 5 mg daily and Risedronate 75 mg two consecutive days per month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 24 months were 0.2% and 0.8% for serum calcium, -1.9% and -1.3% for phosphate, and -10.4% and -17.2% for PTH, respectively. Compared to the Risedronate 5 mg daily group, Risedronate 75 mg two consecutive days per month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (4.5% versus 3.0%). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Once-a-Month

The safety of Risedronate 150 mg administered once a month for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicenter study in postmenopausal women aged 50 to 88 years. The duration of the trial was one year, with 642 patients exposed to Risedronate 5 mg daily and 650 exposed to Risedronate 150 mg once-a month. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H2 antagonists were included in this clinical trial. All women received 1000 mg of elemental calcium plus up to 1000 international units of vitamin D supplementation per day.

The incidence of all-cause mortality was 0.5% for the Risedronate 5 mg daily group and 0.0% for the Risedronate 150 mg once-a-month group. The incidence of serious adverse events was 4.2% in the Risedronate 5 mg daily group and 6.2% in the Risedronate 150 mg once-a-month group. The percentage of patients who withdrew from treatment due to adverse events was 9.5% in the Risedronate 5 mg daily group and 8.6% in the Risedronate 150 mg once-a-month group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 1.1% in the Risedronate 5 mg daily group and 5.2% in the Risedronate 150 mg once-a-month group. These incidence rates are based on reporting of any of 33 acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less. Fever or influenza-like illness with onset within the same period were reported by 0.2% of patients on Risedronate 5 mg daily and 1.4% of patients on Risedronate 150 mg once-a-month.

Gastrointestinal Adverse Events: A greater percentage of patients experienced diarrhea with Risedronate 150 mg once-a-month compared to 5 mg daily (8.2% versus 4.7%, respectively). The Risedronate 150 mg once-a-month group resulted in a higher incidence of discontinuation due to abdominal pain upper (2.5% versus 1.4%) and diarrhea (0.8% versus 0.0%) compared to the Risedronate 5 mg daily regimen. All of these events occurred within a few days of the first dose. The incidence of vomiting that led to discontinuation was the same in both groups (0.3% versus 0.3%).

Ocular Adverse Events: None of the patients treated with Risedronate 150 mg once-a-month reported ocular inflammation such as uveitis, scleritis, or iritis; 2 patients treated with Risedronate 5 mg daily reported iritis.

Laboratory Test Findings: When Risedronate 5 mg daily and Risedronate 150 mg once-a-month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 12 months were 0.1% and 0.3% for serum calcium, -2.3% and -2.3% for phosphate, and 8.3% and 4.8% for PTH, respectively. Compared to the Risedronate 5 mg daily regimen, Risedronate 150 mg once-a-month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (0.2% versus 2.2%). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Prevention of Postmenopausal Osteoporosis

Daily Dosing

The safety of Risedronate 5 mg daily in the prevention of postmenopausal osteoporosis was assessed in two reported randomized, double-blind, placebo-controlled trials. In one study of postmenopausal women aged 37 to 82 years without osteoporosis, the use of estrogen replacement therapy in both placebo-and Risedronate-treated patients was included. The duration of the trial was one year, with 259 exposed to placebo and 261 patients exposed to Risedronate 5 mg. The second study included postmenopausal women aged 44 to 63 years without osteoporosis. The duration of the trial was one year, with 125 exposed to placebo and 129 patients exposed to Risedronate 5 mg. All women received 1000 mg of elemental calcium per day.

In the reported trial with estrogen replacement therapy, the incidence of all-cause mortality was 1.5% for the placebo group and 0.4% for the Risedronate 5 mg group. The incidence of serious adverse events was 8.9% in the placebo group and 5.4% in the Risedronate 5 mg group. The percentage of patients who withdrew from treatment due to adverse events was 18.9% in the placebo group and 10.3% in the Risedronate 5 mg group. Constipation was reported by 1.9% of the placebo group and 6.5% of Risedronate 5 mg group.

In the second reported trial, the incidence of all-cause mortality was 0.0% for both groups. The incidence of serious adverse events was 17.6% in the placebo group and 9.3% in the Risedronate 5 mg group. The percentage of patients who withdrew from treatment due to adverse events was 6.4% in the placebo group and 5.4% in the Risedronate 5 mg group. Nausea was reported by 6.4% of patients in the placebo group and 13.2% of patients in the Risedronate 5 mg group.

Once-a-Week Dosing There were no deaths in a 1-year, double-blind, placebo-controlled study of Risedronate 35 mg once-a-week for prevention of bone loss in 278 postmenopausal women without osteoporosis. More treated subjects on Risedronate reported arthralgia (placebo 7.8%; Risedronate 13.9%), myalgia (placebo 2.1%; Risedronate 5.1%), and nausea (placebo 4.3%; Risedronate 7.3%) than subjects on placebo.

Postmarketing Experience

Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions

Hypersensitivity and skin reactions have been reported, including angioedema, generalized rash, bullous skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal Adverse Events

Events involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported

Musculoskeletal Pain

Bone, joint, or muscle pain, described as severe or incapacitating, have been reported rarely

Eye Inflammation

Reactions of eye inflammation including iritis and uveitis have been reported rarely.

Jaw Osteonecrosis

Osteonecrosis of the jaw has been reported rarely

Pulmonary

Asthma exacerbations

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 any point of contact of Torrent Pharma available at https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Treatment of asymptomatic hypercalcaemia. 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 / dl. A high calcium level in the dialysate may contribute to the development of hypercalcaemia. 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. Hypercalcaemia 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 faecal 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. Hypercalcaemia 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. Decreases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Milk or antacids containing calcium should be given to bind Risedronate and reduce absorption of the drug.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. Standard procedures that are effective for treating hypocalcemia, including the administration

of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

Lethality after single oral doses was seen in female rats at 903 mg/kg and male rats at 1703 mg/kg. The minimum lethal dose in mice and rabbits was 4000 mg/kg and 1000 mg/kg, respectively. These values represent 320 to 620 times the 30 mg human dose based on surface area (mg/m^2).

5. Pharmacological properties

5.1 Mechanism of Action

Calcitriol

Calcitriol is the most active known form of vitamin D_3 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.

Risedronate sodium

Risedronate has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, Risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (for example, lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that Risedronate treatment reduces bone turnover (activation frequency, that is, the rate at which bone remodelling sites are activated) and bone resorption at remodeling sites**.**

Calcium carbonate

Calcium is a major substrate for mineralization and has an antiresorptive effect on bone. Calcium suppresses PTH secretion and decreases bone turnover. Increased levels of PTH are known to contribute to age-related bone loss, especially at cortical sites, while increased bone turnover is an independent risk factor of fractures.

Zinc Sulfate

Adequate zinc is required for normal growth and tissue repair. Urinary elimination of zinc is increased in osteoporotic women. Zinc depletion is shown to diminish the response of oral calcitriol when administered orally. Supplementary zinc not only improves calcitriol response but also helps to arrest bone loss in old postmenopausal women.

5.2 Pharmacodynamic properties

Calcitriol is the most active known form of vitamin D_3 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 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.

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 established post-menopausal osteoporosis, 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.

Risedronate

Risedronate treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In reported clinical trials, administration of Risedronate to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone-specific alkaline phosphatase (a marker of bone formation). At the 5 mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone-specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of Risedronate for the treatment of osteoporosis in postmenopausal women, Risedronate 5 mg daily and Risedronate 35 mg once-a-week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the Risedronate 5 mg daily and Risedronate 35 mg once-a-week groups, respectively. When postmenopausal women with osteoporosis were treated for 1 year with Risedronate 5 mg daily or Risedronate 75 mg two consecutive days per month, urinary collagen cross-linked N-telopeptide was decreased by 54% and 52%, respectively, and serum bone-specific alkaline phosphatase was reduced by 36% and 35%, respectively. In a 1–year study comparing Risedronate 5 mg daily versus Risedronate 150 mg once-a-month in women with postmenopausal osteoporosis, urinary collagen cross-linked N-telopeptide was decreased by 52% and 49%, respectively, and serum bone-specific alkaline phosphatase was reduced by 31% and 32%, respectively.

5.3 Pharmacokinetic properties

Calcitriol

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1µg Calcitriol in healthy subjects were found within 2-6 hours.

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.

Metabolism

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 at least 4 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.

Risedronate

Absorption

Based on simultaneous modeling of serum and urine data, peak absorption after an oral dose is achieved at approximately 1 hour (Tmax) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, from 2.5 mg to 30 mg; multiple dose, from 2.5 mg to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution.

Food Effect

The extent of absorption of a 30 mg dose (three 10 mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. calcitriol is effective when administered at least 30 minutes before breakfast.

Distribution

The mean steady-state volume of distribution for Risedronate is 13.8 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] Risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of Risedronate in soft tissues was in the range of 0.001% to 0.01%.

Metabolism

There is no evidence of systemic metabolism of Risedronate.

Excretion

In young healthy subjects, approximately half of the absorbed dose of Risedronate was excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modeling of serum and urine data, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the

difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. In osteopenic postmenopausal women, the terminal exponential half-life was 561 hours, mean renal clearance was 52 mL/min (CV = 25%), and mean total clearance was 73 mL/min (CV = 15%).

Specific Populations

Pediatric: calcitriol is not indicated for use in pediatric patients.

Gender: Bioavailability and pharmacokinetics following oral administration are similar in men and women.

Geriatric: Bioavailability and disposition are similar in elderly (greater than 60 years of age) and younger subjects. No dosage adjustment is necessary.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Impairment: Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of Risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min. Risedronate is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 30 mL/min.

Hepatic Impairment: No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (less than 0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

Drug Interactions: No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (Cytochrome P450).

Calcium Carbonate

Calcium carbonate is converted to calcium chloride by gastric hydrochloric acid in stomach. 39% of calcium is absorbed from 0.5 - 1.4 g dose of calcium carbonate. Absorption of Calcium depends upon previous intake of Calcium, other nutrients, pregnancy, lactation, overall calcium balance and availability of vitamin D or it's analogues. Calcium carbonate is absorbed as free Calcium and not metabolised. Approximately half the Calcium in serum is protein bound, 5 - 10 % complexed in the form of small readily diffusible organic salts and the remaining as free ions.

Zinc sulphate.

20% to 30% of dietary Zinc is absorbed from the GI tract. The main excretion route is through the intestine. Only minor amounts are lost in urine (~2%).

6. Nonclinical properties

Calcitriol

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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, rats were administered daily oral doses up to approximately 8 times the maximum recommended human daily dose. There were no significant drug-induced tumor findings in male or female rats. The high dose male group was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses approximately 6.5 times the human dose. There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow. Risedronate was positive in a chromosomal aberration assay in CHO cells at highly cytotoxic concentrations (greater than 675 mcg/mL, survival of 6% to 7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose approximately 5 times the human dose. Decreased implantation was noted in female rats treated with doses approximately 2.5 times the human dose. In male rats, testicular and epididymal atrophy and inflammation were noted at approximately 13 times the human dose. Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses approximately 5 times the human dose. There was moderate-tosevere spermatid maturation block after 13 weeks in male dogs at an oral dose approximately 8 times the human dose. These findings tended to increase in severity with increased dose and exposure time.

Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (mg/m2). Actual doses were 24 mg/kg/day in rats, 32 mg/kg/day in mice, and 8, 16 and 40 mg/kg/day in dogs.

6.1 Animal toxicology or Pharmacology

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at daily oral doses up to 4 and 25 times the human recommended oral dose of 5 mg for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, Risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.5 to 1.5 times the 5 mg/day human daily dose.

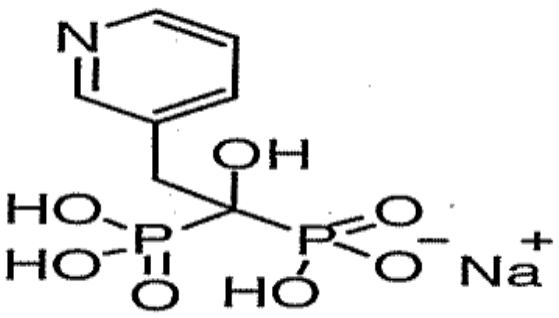
In dogs treated with an oral dose approximately 5 times the human daily dose, Risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose approximately 0.5 times the human daily dose.

The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that Risedronate did not interfere with bone mineralization even at the highest dose tested, which was approximately 3500 times the lowest antiresorptive dose in this model (1.5 mcg/kg/day) and approximately 800 times the human daily dose of 5 mg. This indicates that calcitriol administered at the therapeutic dose is unlikely to induce osteomalacia. Dosing multiples provided above are based on the recommended human dose of 5 mg/day and normalized using body surface area (mg/m2).

7 Description

Risedronate Sodium Hemi-pentahydrate

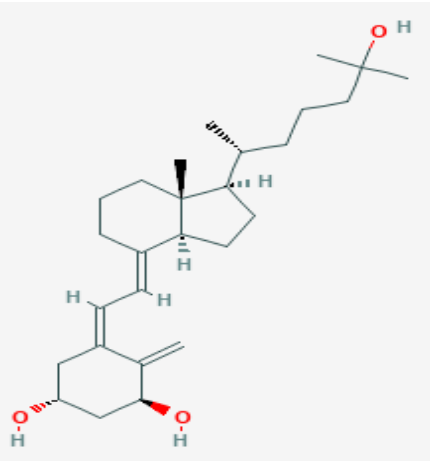
Risedronate Sodium is 1-Hydroxy-2-(3-pyridyl) ethane-1,1-diylbis(phosphonic acid) monosodium salt with empirical formula $C_7H_{10}NNaO_7P_2$, 2.5 H_2O and molecular weight 350.1. The chemical structure is:



Risedronate is a White o off- white powder. It is soluble in water and in aqueous solution; insoluble in common organic solvents.

Calcitriol

Calcitriol is a synthetic physiologically active analog of vitamin D, specifically the vitamin D3 form. It is chemically, (1*R*,3*S*,5*Z*)-5-[(2*E*)-2-[(1*R*,3*aS*,7*aR*)-1-[(2*R*)-6-hydroxy-6-methylheptan-2-yl]-7*a*-methyl-2,3,3*a*,5,6,7-hexahydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidenecyclo hexane-1,3-diol with molecular weight of 416.6 g/mol and empirical formula is $C_{27}H_{44}O_3$. The chemical structure is:



Calcium

Calcium is a mineral that is present naturally in the food. Calcium is an element with atomic symbol Ca, atomic number 20, and atomic weight 40.08.

Zinc

Zinc is an essential mineral and heavy metal that is included in most over-the-counter multivitamin and mineral supplements. The molecular formula is Zn and molecular weight is 65.4g/mol.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Gemitrol kit is packed in blister strips 1 tablet and 6 capsules.

8.4 Storage and handing instructions.

Store at a temperature not exceeding 25 ºC in a dry place, protected from light.

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10 Details of manufacturer

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA

At:Plot No. 708/6,

Behind Somnath Temple, Somnath Road,

Dabhel Village, Nani Daman-396 215

11 Details of permission or licence number with date

Mfg licence for Tablet MNB/05/183 issued on 16.07.2018

Mfg licence for Capsules DD/L/664 issued on 16.07.2018

12.Date of revision

SEP 2024

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/GEMITROL KIT- 35 mg and 0.25 mcg+200 mg+7.5 mg /Sep-2024/03/PI