

Rantum^{2g} Sachet

(Strontium Ranelate)

رینٹیم
۲ گرام
ساشے
(سٹرونٹیم رینیلےٹ)

COMPOSITION

Rantum Sachet 2g

Each sachet contains:

Strontium ranelate (MS).....2g

DESCRIPTION

Strontium ranelate is used to treat osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures, in men at increased risk of fracture.

INDICATIONS AND USAGE

- Treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures.
- Treatment of severe osteoporosis in adult men at increased risk of fracture.

CLINICAL PHARMACOLOGY

• Mechanism of Action

Increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture.

Reduces bone resorption by decreasing osteoclast differentiation and resorbing activity.

This results in a rebalance of bone turnover in favor of bone formation.

Strontium ranelate stimulates the calcium sensing receptors and leads to the differentiation of pre-osteoblast to osteoblast which increases the bone formation. Strontium ranelate also stimulates osteoblasts to secrete osteoprotegerin in inhibiting osteoclast formed from pre-osteoclasts in relation to the receptor activator of nuclear factor kappa-B ligand (RANKL) system, which leads to the decrease of bone resorption.

DOSAGE AND ADMINISTRATION

The recommended dose is one 2g sachet once daily by oral administration.

Due to the nature of the treated disease, strontium ranelate is intended for long-term use.

The absorption of strontium ranelate is reduced by food, milk and derivative products and therefore, strontium ranelate should be administered in-between meals. Given the slow absorption, strontium ranelate should be taken at bedtime, preferably at least two hours after eating.

Patients treated with strontium ranelate should receive vitamin D and calcium supplements if dietary intake is inadequate.

Treatment should only be initiated by a physician with experience in treating osteoporosis.

Elderly Patients

The efficacy and safety of strontium ranelate have been established in a broad age range (up to 100 years at inclusion) of postmenopausal women with osteoporosis. No dose adjustment is required in relation to age.

Patients with Renal Impairment

Strontium ranelate is not recommended for patients with severe renal impairment (creatinine clearance below 30ml/min). No dose adjustment is required in patients with mild-to-moderate renal impairment (30-70ml/min creatinine clearance).

Patients with Hepatic Impairment

As strontium ranelate is not metabolised, no dose adjustment is required in patients with hepatic impairment.

Paediatric Population

The safety and efficacy of strontium ranelate in children aged below 18 years have not been established. No data is available.

Method of Administration

For oral use.

The powder in the sachets must be taken as a suspension in a glass containing a minimum of 30 ml (approximately one third of a standard glass) of water.

Although in-use studies have demonstrated that strontium ranelate is stable in suspension for 24 hours after preparation, the suspension should be drunk immediately after being prepared.

PHARMACOKINETICS

The absorption, distribution and binding to plasma proteins of ranelic acid are low due to its high polarity. There is no accumulation of ranelic acid and no evidence of metabolism in animals and humans. Absorbed ranelic acid is rapidly eliminated unchanged via the kidneys.

• Absorption

The absolute bioavailability of strontium is about 25% (range 19-27%) after an oral dose of 2 g strontium ranelate. Maximum plasma concentrations are reached 3-5 hours after a single dose of 2 g. Steady state is reached after 2 weeks of treatment. Intake of strontium, ranelate with calcium or food reduces the bioavailability of strontium by approximately 60-70%, compared with administration 3 hours after a meal. Due to the relatively slow absorption of strontium, food and calcium intake should be avoided both before and after administration of strontium ranelate. Oral supplementation with vitamin D has no effect on strontium exposure.

• Distribution

Strontium has a volume of distribution of about 1L/kg. The binding of strontium to human plasma proteins is low (25%) and strontium has a high affinity for bone tissue. Measurement of strontium concentration in iliac crest bone biopsies from patients treated for up to 60 months with strontium ranelate 2 g/day indicate that bone strontium concentrations may reach a plateau after about 3 years of treatment. There are no data in patients to demonstrate elimination kinetics of strontium from bone off-therapy.

• Metabolism

As a divalent cation, strontium is not metabolised. Strontium ranelate does not inhibit cytochrome P450 enzymes.

• Excretion

The excretion of strontium is time and dose independent. The effective half-life of strontium is about 60 hours. * Strontium excretion occurs via the kidneys and the gastrointestinal tract. Its plasma clearance is about 12 ml/min (CV 22%) and its renal clearance about 7 ml/min (CV 28%).

OVERDOSAGE

Symptoms

The repeated administration of 4 g strontium ranelate per day over 25 days in healthy postmenopausal women, good tolerance

was shown. Single administration of doses up to 11 g in healthy young male volunteers did not cause any particular symptoms.

Management

Administration of milk or antacids may be helpful to reduce the absorption of the active substance. In the event of substantial overdose, vomiting may be considered to remove unabsorbed active substance.

ADVERSE REACTIONS

Adverse reactions were usually mild and transient. Common: nausea, diarrhoea, loose stools, headache, disturbances in consciousness memory loss, dermatitis and eczema, venous thromboembolism, blood creatinine kinase increased. Uncommon: seizures. Rare: DRESS. Very rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis. Frequency-unknown: bone marrow failure, hypersensitivity skin reactions (rash, eosinophilia, lymphadenopathy, pruritus, urticaria, angioedema), hepatitis.

WARNINGS AND PRECAUTIONS

• Cardiac Ischemic Events

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration. Treatment should be stopped if the patient develops ischemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled.

• Use in Patients with Renal Impairment

In the absence of bone safety data in patients with severe renal impairment treated with strontium ranelate, strontium ranelate is not recommended in patients with a creatinine clearance below 30ml/min. Periodic assessment of renal function is recommended in patients with chronic renal impairment. Continuation of treatment with strontium ranelate in patients developing severe renal impairment should be considered on an individual basis.

• Venous Thromboembolism

Strontium ranelate treatment was associated with an increase in the annual incidence of venous thromboembolism (VTE), including pulmonary embolism. The cause of this finding is unknown. Strontium ranelate should be used with caution in patients at increased risk of VTE, including patients with a history of VTE.

• Skin Reactions

Cases of severe hypersensitivity syndromes, including, in particular, drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, have been reported with the use of strontium ranelate. The DRESS syndrome is characterized by rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease). Time to onset was usually around 3-6 weeks and the outcome in most cases favourable upon discontinuation of strontium ranelate and after initiation of corticosteroid therapy. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy. Patients should be informed to stop strontium ranelate immediately and permanently when a rash occurs and to seek medical advice. Patients who have stopped treatment due to hypersensitivity reactions or other serious allergic reactions should not re-start therapy with strontium ranelate.

Pregnancy

There are no data from the use of strontium ranelate in pregnant women. If strontium ranelate is used inadvertently during

pregnancy, treatment must be stopped.

Nursing Mothers

Strontium is excreted in milk. Strontium ranelate should not be given to nursing women.

DRUG INTERACTIONS

Drugs, food, milk and derivative products containing calcium may reduce the bioavailability of strontium ranelate by approximately 60-70%. Therefore, administration of strontium ranelate should be separated by at least two hours. Administration of aluminium and magnesium hydroxides either two hours before or together with strontium ranelate caused a slight decrease in the absorption of strontium ranelate (20-25% AUC decrease), while absorption was almost unaffected when the antacid was given two hours after strontium ranelate. It is therefore preferable to take antacids at least two hours after strontium ranelate.

Simultaneous administration of strontium ranelate with oral tetracycline and quinolone antibiotics is not recommended because divalent cations can form complexes with oral tetracycline and quinolone antibiotics at the gastro-intestinal level and thereby reduce their absorption. No interaction was observed with oral supplementation of vitamin D.

No evidence of clinical interactions or relevant increase of blood strontium levels with medicinal products expected to be commonly prescribed concomitantly with strontium ranelate. These included nonsteroidal anti-inflammatory agents (including acetylsalicylic acid), anilides (such as paracetamol), H2 blockers and proton pump inhibitors, diuretics, digoxin and cardiac glycosides, organic nitrates and other vasodilators for cardiac diseases, calcium channel blockers, beta blockers, ACE inhibitors, angiotensin II antagonists, selective beta-2 adrenoceptor agonist, oral anticoagulants, platelet aggregation inhibitors, statins, fibrates and benzodiazepine derivatives.

STORAGE & INSTRUCTIONS:

Store between 15-25°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

Rantum Sachet 2g

7's Sachets.

خوراک و طبیعتہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دھوپ، گرمی،

نمی سے محفوظ اور بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخے پر

فروخت کریں۔

Manufactured by:

**PHARMASOL
PRIVATE LIMITED**

Plot # 549, Sundar Industrial Estate,
Lahore, Pakistan.