ONITA®
(Strontium Ranelate)

2g Sachet

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COMPOSITION
ONITA granules for oral suspension
Each sachet contains:
Strontium ranelate…….. 2gm
(PharmEvo Specs.)

DESCRIPTION
ONITA contains Strontium ranelate, a strontium (II) salt of ranelic acid which is used for the treatment of osteoporosis. Strontium ranelate is made up of 2 atoms of stable strontium and 1 molecule of ranelic acid, the organic part permitting the best compromise in terms of molecular weight, pharmacokinetics and acceptability of the drug. It is chemically designated as distrontium 5-[bis (2-oxido-2-oxoethyl) amino]-4-cyano-3-(2-oxido-2-oxoethyl) thiophene-2-carboxylate and molecular formula is $C_{12}H_6N_2O_8SSr_2$

CLINICAL PHARMACOLOGY

Mechanism of Action

In vitro, strontium ranelate:
- 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.

Pharmacokinetics

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 1 L/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 metabolized. Strontium ranelate does not inhibit cytochrome P450 enzymes.

Excretion
The elimination 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 and its renal clearance about 7 ml/min.

INDICATIONS

ONITA is indicated in treatment of severe osteoporosis:
- In postmenopausal women,
- In adult men,
at high risk of fracture, for whom treatment with other drugs approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.

In postmenopausal women, strontium ranelate reduces the risk of vertebral and hip fractures.

DOSAGE AND ADMINISTRATION

The recommended dose is one 2 g 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.

Dose adjustment and dosing considerations in Special populations

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

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment

Administration requirements
ONITA sachet is for oral use. The granules 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. Strontium ranelate is stable in suspension for 24 hours after preparation; the suspension should be drunk immediately after being prepared.

CONTRAINDICATIONS

- Hypersensitivity to strontium ranelate.
- Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.
- Temporary or permanent immobilization due to e.g. post-surgical recovery or prolonged bed rest.
- Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Uncontrolled hypertension.

WARNINGS AND PRECAUTIONS

Cardiac ischemic events
In pooled randomized placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in Strontium ranelate treated patients compared to placebo. Before starting treatment, patients should be evaluated with respect to cardiovascular risk. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should only be treated with strontium ranelate after careful consideration. During Strontium ranelate treatment, these cardiovascular risks should be monitored on a regular basis generally every 6 to 12 months. Treatment should be stopped if the patient develops ischemic heart disease, peripheral arterial disease, and cerebrovascular disease or if hypertension is uncontrolled.

Venous thromboembolism
Strontium ranelate treatment has been associated with an increase in the annual incidence of venous thromboembolism (VTE), including pulmonary embolism. Strontium ranelate is contra-indicated in patients with a past history of venous thromboembolic events and should be used with caution in patients at risk of VTE. Strontium ranelate should be discontinued as soon as possible in the event of an illness or a condition leading to immobilization and adequate preventive measures taken. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. When a VTE occurs, Strontium ranelate should be stopped.

Renal impairment patients
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 30 ml/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.

Skin reactions
Life-threatening cutaneous reactions [Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS)] have been reported with the use of Strontium ranelate. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease) are present, Strontium ranelate treatment should be discontinued immediately. If the patient has developed SJS, TEN or DRESS with the use of Strontium ranelate, it must not be re-started in this patient at any time.

The best results in managing SJS, TEN or DRESS come from early diagnosis

and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. The outcome of DRESS is favourable in most cases upon discontinuation of Strontium ranelate and after initiation of corticosteroid therapy when necessary. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy.

Interaction with laboratory test
Strontium interferes with colorimetric methods for the determination of blood and urinary calcium concentrations. Therefore, in medical practice, inductively coupled plasma atomic emission spectrometry or atomic absorption spectrometry methods should be used to ensure an accurate assessment of blood and urinary calcium concentrations.

ADVERSE REACTIONS

Blood and lymphatic disorders
Uncommon: Lymphadenopathy (in association with hypersensitivity skin reactions)
Rare: Bone marrow failure, Eosinophilia (in association with hypersensitivity skin reactions)
Metabolism and nutrition disorders
Common: Hypercholesterolemia
Psychiatric disorders
Common: Insomnia
Uncommon: Confusion
Nervous system disorders
Common: Headache, Disturbances in consciousness, Memory loss, Dizziness, Paraesthesia
Uncommon: Seizures
Ear and labyrinth disorders
Common: Vertigo
Cardiac disorders
Common: Myocardial infarction
Vascular disorders
Common: Venous thromboembolism (VTE)
Respiratory, thoracic and mediastinal disorders
Common: Bronchial hyper reactivity
Gastrointestinal disorders
Common: Nausea, Diarrhea and Loose stools, Vomiting, Abdominal pain, gastrointestinal pain, Gastro esophageal reflux, Dyspepsia, Constipation, Flatulence
Uncommon: Oral mucosal irritation (stomatitis and/or mouth ulceration), Dry mouth
Hepatobiliary disorders
Common: Hepatitis
Uncommon: Serum transaminase increased (in association with hypersensitivity skin reactions)
Skin and subcutaneous tissue disorders
Very common: Hypersensitivity skin reactions (rash, pruritus, urticaria, angioedema)
Common: Eczema
Uncommon: Dermatitis, Alopecia
Rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Very rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders
Very common: Musculoskeletal pain (muscle spasm, myalgia, bone pain, arthralgia and pain in extremity)
General disorders and administration site conditions
Common: Peripheral edema
Uncommon: Pyrexia (in association with hypersensitivity skin reactions), Malaise
Investigations
Common: Blood Creatine phosphokinase (CPK) increased

DRUG INTERACTIONS

• Food, milk and derivative products, and drugs containing calcium may reduce the bioavailability of strontium ranelate by approximately 60-70%. Therefore, administration of strontium ranelate and such products should be separated by at least two hours.
• As divalent cations can form complexes with oral tetracycline (e.g. doxycycline) and quinolone antibiotics (e.g. ciprofloxacin) at the gastro-intestinal level and thereby reduce their absorption, simultaneous administration of strontium ranelate with these drugs is not recommended. As a precautionary measure, Strontium ranelate treatment should be suspended during treatment with oral tetracycline or quinolone antibiotics.
• 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. However, when this dosing regimen is impractical due to the recommended administration of Strontium ranelate at bedtime, concomitant intake remains acceptable.

USE IN SPECIAL POPULATIONS

Pregnancy
There is no data from the use of strontium ranelate in pregnant women. At high doses; animal studies have shown reversible bone effects in the offspring during pregnancy. If strontium ranelate is used inadvertently during pregnancy, treatment must be stopped.

Nursing mothers
Strontium ranelate should not be used during breast-feeding due to excretion of Strontium ranelate in human milk.

Pediatrics
The safety and efficacy of strontium ranelate in children aged below 18 years have not been established.

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

Renal impairment
In patients with mild-to-moderate renal impairment (30-70 ml/min creatinine clearance), strontium clearance decreases as creatinine clearance decreases (approximately 30% decrease over the creatinine clearance range 30 to 70 ml/min) and thereby induces an increase in strontium plasma levels.
No dose adjustment is required in patients with mild-to-moderate renal impairment (30-70 ml/min creatinine clearance) (See WARNING & PRECAUTIONS and DOSAGE & ADMINISTRATION)
There is no pharmacokinetic data in patients with severe renal impairment (creatinine clearance below 30 ml/min)

Hepatic impairment
There is no pharmacokinetic data in patients with hepatic impairment. Due to the pharmacokinetic properties of strontium, no effect is expected. No dose adjustment is required in patients with hepatic impairment (See DOSAGE & ADMINISTRATION)

OVER DOSAGE

Symptoms
Good tolerance was shown in a clinical study investigating the repeated administration of 4 g strontium ranelate per day over 25 days in healthy postmenopausal women. 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.

PRESENTATION

Onita Sachet is available in pack of 7 sachets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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DI: ONIA11/2016