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Strontium ranelate in post-menopausal osteoporosis

Ranelinian strontu w osteoporozie pomenopauzalnej

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Abstract

Strontium ranelate is one of the first-line agents with proven anti-fracture activity used in the therapy of post-menopausal osteoporosis. Its mechanism of action makes it, however, different from other drugs, since it simultaneously stimulates two reverse processes: bone formation and bone resorption. The action of the agent depends on various mechanisms, including the activation of calcium receptors, localised on osteoblasts and osteoclasts, and on the influence on the OPG/RANKL system. The drug effectively prevents spinal, hip and extravertebral fractures. The agent's anti-fracture efficacy within the spine does not depend on the patient's age, or on base BMD values, or on the concentration of bone metabolism markers. As to the anti-fracture efficacy in the hip, it concerns women with an increased bone fracture risk. Strontium ranelate increases bone mineral density within the lumbar spine and the hip, decreases the concentrations of bone resorption markers, and increases the concentrations of bone formation markers. The drug is administered in a daily 2.0 g oral dose.
This paper presents indications to therapy with strontium ranelate, specifying also its side effects and contraindications. We compare the anti-fracture efficacy of strontium ranelate to the efficacy of other agents of proven anti-fracture activity, based on published clinical studies. **(Pol J Endocrinol 2011; 62 (1): 65–72)**

Key words: *treatment, osteoporosis, strontium ranelate*

Streszczenie

Ranelinian strontu jest lekiem pierwszego rzutu o udowodnionej aktywności przeciwzłamaniowej w leczeniu osteoporozy pomenopauzalnej. Mechanizm działania wyróżnia go spośród innych leków, wpływa bowiem jednocześnie na pobudzenie tworzenia i hamowanie resorpcji kości. Działanie leku zależy od różnych mechanizmów, w tym od aktywacji receptorów wapniowych zlokalizowanych na osteoblastach i osteoklastach i wpływu na system OPG/RANKL. Lek jest skuteczny w zapobieganiu złamaniom kręgosłupa, biodra i złamaniom pozakręgowym. Skuteczność przeciwzłamaniowa w zakresie kręgosłupa nie zależy od wieku pacjentów, wyjściowych wartości gęstości mineralnej kości oraz stężenia markerów metabolizmu kostnego. Skuteczność przeciwzłamaniowa w zakresie biodra dotyczy kobiet o zwiększonym ryzyku złamania kości. Ranelinian strontu zwiększa gęstość mineralną kości w zakresie kręgosłupa lędźwiowego i biodra, obniża stężenie markerów resorpcji kości i podwyższa stężenie markerów tworzenia kości. Lek podaje się w codziennej dawce 2,0 doustnie. W opracowaniu omówiono wskazania do leczenia ranelinianem strontu, przeciwwskazania, działanie niepożądane leku, a także porównano jego skuteczność do innych leków o udowodnionej aktywności przeciwzłamaniowej na podstawie przeprowadzonych badań klinicznych. **(Endokrynol Pol 2011; 62 (1): 65–72)**

Słowa kluczowe: *leczenie, osteoporoza, ranelinian strontu*

Introduction

Strontium ranelate is a medical agent of proven anti-fracture effectiveness which is used in the therapy of post-menopausal osteoporosis as a first-line drug. The longest observation of the drug's efficacy has been eight years.

Strontium ranelate structure and mechanism of action

Strontium ranelate consists of an organic part (ranelic acid) and two atoms of stable, non-radioactive strontium. It is the only drug used in osteoporosis therapy which demonstrates a dual mode of action towards bone metabolism: it supports bone formation (osteogenesis), stimulating the division of osteoblast precursor and collagen synthesis, as well as the synthesis of non-collagen proteins in osteoblasts, while simultaneously decreasing bone resorption by inhibiting the activity and differentiation of osteoclasts.

Several reports have been published looking at the various mechanisms of strontium ranelate activity.

Calcium receptor

In studies on animals, a positive effect of strontium ranelate has been noted on the proliferation, differentiation and mineralisation of osteoblasts by activation of calcium receptors on their surface, that effect being proportional to the therapy period and the dose of the administered drug [1, 2]. Strontium ranelate stimulates phosphoryla-

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tion and, consequently, the activation of intracellular kinase of mouse osteoblasts (ERK, extracellular signal-regulated kinase), and also increases the expression of osteocalcin mRNA and bone morphogenetic protein-2.

In another study, also on animals, strontium ranelate was observed on cells of mature osteoblasts to accelerate their apoptosis proportionally to drug dose [3]. That effect is obtained via calcium receptors on the osteoclast surface, triggering a cascade of intracellular transformations, which eventually leads to osteoclast apoptosis. The combined action of calcium and strontium ranelate on calcium receptors exerts a much stronger effect on osteoclast apoptosis than each individual factor acting alone.

Akt

Studies on mice [4] have demonstrated strontium ranelate effects on osteoblast survival prolongation (increased proliferation and reduced apoptosis) to also depend on the activation of the Akt kinase-related pathway of changes. Akt kinase plays a certain role in cellular processes, including glucose metabolism and cell proliferation and apoptosis.

Prostaglandins (PGE2)

Studies on mice [4] have demonstrated that the effect of strontium ranelate on the proliferation and reduced apoptosis of osteoblasts was neutralised by selective inhibition of cyclooxygenase-2 (COX-2). The results indicated that the positive effect of strontium ranelate on osteoblasts depends also on how much it influences PGE2 production.

OPG/RANKL system (osteoprotegerin/ligand of the receptor nuclear activator of kappa B factor)

A positive effect of strontium ranelate was observed on the OPG/RANKL ratio, causing an increased secretion of osteoprotegerin and its more pronounced activity with a simultaneous reduction of RANKL expression, leading to suppression of osteoblast-induced osteoclastogenesis. A positive effect of strontium ranelate was found with regards to maturation of human osteoblasts and differentiation of osteocytes [5].

Insulin-like growth factor

In the course of a six-month therapy with strontium ranelate at a daily dose of 2.0 g, an increase of the insulin-like growth factor (IGF-1) concentration was obtained [6]. It is assumed that IGF deficit plays a definite role in the development of post-menopausal osteoporosis and its administration may exert an advantageous influence on BMD increase.

The most significant clinical studies on strontium ranelate in the therapy of osteoporosis

STRATOS study

The Strontium Ranelate for Treatment of Osteoporosis (STRATOS) study demonstrated that strontium ranelate increases bone mineral density in the lumbar spine, decreasing the incidence of new spinal fractures. The daily 2.0 g dose of strontium ranelate was accepted as the most effective mode of post-menopausal osteoporosis treatment [7].

A randomised, double-blind study with placebo control was performed over two years in 353 post-menopausal women with, at least, one identified vertebral fracture in their history and a T-score in the lumbar spine < -2.4. The enrolled patients received 0.5, 1.0 or 2.0 g of strontium ranelate daily or a placebo.

Bone mineral density in the lumbar spine demonstrated a dose-proportional, rising tendency in the strontium ranelate-treated group vs. the placebo group. The incidence of spinal fractures fell during the second year of observation. The activity of alkaline phosphatase bone fraction (a bone formation marker) increased after strontium ranelate treatment and the concentration of NTx (N-terminal cross-linked telopeptide of type-I collagen, a bone resorption marker) decreased vs. the placebo group.

SOTI study

In the Spinal Osteoporosis Therapeutic Intervention (SOTI) study, strontium ranelate was demonstrated to be an agent already effective in spinal fracture prevention after one year of therapy in post-menopausal women with advanced osteoporosis [8].

A group of 1,649 women (> 50) with post-menopausal osteoporosis and, at least, one osteoporotic vertebral fracture in their history and lumbar spine BMD ≤ 0.840 g/cm^2 (Hologic) were enrolled into a three-year, randomised, double-blind and placebo-controlled study. The patients received strontium ranelate at a daily dose of 2.0 g or a placebo. They were also supplemented with calcium (up to 1,000 mg daily according to diet) and vitamin D_3 (400–800 IU/d). The study was preceded by a period lasting from two weeks to six months (Fracture International Run-in for Protelos — FIRST programme), in which calcium and vitamin D_3 deficits measured by serum 25(OH)D_3 concentration, were supplemented.

A 41% decrease in the incidence of new spinal fractures was found vs. the placebo group ($p < 0.001$) and a 14.4% BMD increase in the lumbar spine vs. the placebo group. A lower incidence of new fractures was confirmed already after one year of treatment (fracture incidence reduction > 49% vs. the placebo group).

TROPOS study

The Treatment Of Peripheral Osteoporosis (TROPOS) study demonstrated strontium ranelate to be an agent that significantly reduced the all-extravertebral fracture risk during three years of treatment. It significantly decreased the risk of hip fractures in patients particularly endangered by such events (age ≥ 74 years and T-score ≤ –3.0) during three years of treatment. It reduced the number of spinal fractures after the first year of therapy, with that effect maintained for the entire three years of treatment, in patients with and without a vertebral fracture in their history [9].

A group of 5,091 women aged > 74 years or 70–74 years with at least one bone fracture risk factor (osteoporotic fracture during post-menopausal period, stay at a nursing home, osteoporotic fracture in history of patient's mother) and with femoral neck BMD ≤ 0.600 g/cm^2 (Hologic) were enrolled into a five-year, randomised, double-blind and placebo-controlled study. The patients received strontium ranelate at a daily dose of 2.0 g or a placebo. They were also supplemented with calcium (up to 1,000 mg per day according to diet) and vitamin D_3 (400–800 IU per day). The study was preceded by a period from two weeks to six months, the FIRST programme, in which calcium and vitamin D_3 deficits were supplemented, measured by serum 25(OH)D_3 concentration.

After three years of treatment, a 16% decrease was observed in the incidence of all extravertebral fractures ($p = 0.04$). The applied therapy reduced the number of extravertebral (hip, wrist, pelvic, caudal, costal, sternal, clavicular and humeral) fractures, osteoporotic in character, by 19% ($p = 0.031$). The incidence of proximal femoral bone fractures decreased by 15%, although this was statistically insignificant. In the group of women with the highest fracture risk (age ≥ 74 years and T-score ≤ –3.0), the risk of proximal femoral bone fracture decreased by 36% ($p = 0.046$). The number of new vertebral fractures, evaluated by X-ray, fell by 39% ($p < 0.001$) among all the patients, and by 45% among the women without vertebral fracture in their history. In the group of patients treated with strontium ranelate, a more prominent increase of BMD was observed in the femoral neck and the total hip vs. the placebo group.

Strontium ranelate was well tolerated in all the above-mentioned studies, with most symptoms occurring during the first three months of drug administration [9].

The efficacy of strontium ranelate in post-menopausal osteoporosis

This part of the review looks at the efficacy of strontium ranelate in bone fracture prevention, its effects on bone and life quality improvement, and on bone mineral density and the concentration of bone metabolism markers.

Bone fracture prevention

The anti-fracture efficacy of strontium ranelate has been demonstrated in all the skeleton fragments where such efficacy has also been studied in the cases of other drugs.

Thus, strontium ranelate has been effective in:

— the spine [7, 8]: the longest observation period, regarding anti-fracture efficacy within the spine was eight years [10];
— the hip [9];
— extravertebral skeleton fragments [13].

Number Needed to Treat (NNT) — the number of subjects who have to be treated to obtain the assumed effect within a specific period of time for strontium ranelate to prevent vertebral fractures during a three-year therapy period is 9.

Number Needed to Treat for strontium ranelate to prevent hip fractures during a three-year therapy period is 48 [11].

Following a review of the literature concerning third phase studies of medical agents with proven anti-fracture efficacy which are available in Europe, the lowest NNT value was found for strontium ranelate as opposed to all other drugs [11].

Bone quality improvement

Bone quality was evaluated by an analysis of biopsied material. Qualitative and quantitative changes, identified in histomorphometric study, following strontium ranelate therapy, can be responsible for bone quality improvement and fracture risk reduction.

A study performed in 133 women with post-menopausal osteoporosis, treated for 1–5 years with strontium ranelate (2.0 g daily) indicates that changes in osseous microarchitecture may explain the drug's anti-fracture efficacy demonstrated during osteoporosis therapy [12].

Significant changes were found in bone microarchitecture, including: higher thickness of cortical bone, a higher number of osseous trabeculae and smaller spaces between osseous trabeculae in the patients treated with strontium ranelate vs. those in the control group. Also, osteoblast surface was larger after the administration of strontium ranelate vs. the control group. In the group of women receiving strontium ranelate, an increased rate of trabecular bone mineralisation was observed vs. that in the control group. No cortical bone porosity was found in the group treated with strontium ranelate.

Another study [13] found that strontium deposited preferentially in newly formed bone during strontium ranelate treatment with maintained collagen cross-linking. Bone mineralisation was increased mainly as a re-

sult of strontium deposition in bones rather than by changes in calcium content. Bone quality indices were maintained in women with post-menopausal osteoporosis treated with strontium ranelate, combined with calcium and vitamin B.

The presence of strontium only in the newly formed bone after a three-year therapy with strontium ranelate in women with post-menopausal osteoporosis was also confirmed in another report [14]. No more than 0.5–10 calcium atoms were replaced by strontium in hydroxyapatite. The proportion of strontium to calcium atoms in hydroxyapatites did not exceed 1 in 20, while neither the thickness nor the length of hydroxyapatites changed as a result of the applied treatment. No changes in bone quality were found during the treatment apart from the partial replacement of calcium atoms by strontium atoms in newly formed bone.

Life quality improvement

The results of the QUALIOST questionnaire confirmed that three-year therapy with strontium ranelate significantly improved life quality in its emotional and physical aspects vs. placebo [15]. Back pain remission was observed in the majority of the patients vs. the placebo group. Life quality improvement, described in another report [16], was observed in a group of women aged > 80 years treated with strontium ranelate.

Effects on bone mineral density

Strontium ranelate increases bone mineral density in the lumbar spine [7, 8], the femoral neck and in the total hip [9]. It partially depends on the unspecific effects of strontium atoms deposited in the newly formed bone and with an atomic weight > than that of calcium [13].

Effects on the concentration of bone metabolism markers

Strontium ranelate increases the activity of alkaline phosphatase bone fraction in serum (bone formation marker) and, simultaneously, reduces the concentration of NTx (bone resorption marker) [7].

By contrast, no increase was seen in the concentration of bone formation markers (the activity of alkaline phosphatase bone fraction), and there was even a slight reduction of PINP (N-terminal propeptide of procollagen of type I) in serum after three and six months of therapy with strontium ranelate, as described in one of the reports [17].

In whom is strontium ranelate effective in bone fracture prevention in osteoporosis?

In the rest of this review, the presented information concerns the effectiveness of strontium ranelate therapy in reducing bone fracture risk and increasing bone mineral density.

The current FRAX® method, used to evaluate ten-year bone fracture risk and useful in qualifying patients to diagnostic examinations and therapy for osteoporosis, was not known at the time of studies on strontium ranelate (as well as on other drugs). Therefore, patients were qualified for therapy by the presence of bone fractures (in the spine) and on the basis of specific DXA examination results. Analysing the obtained results (very often *post hoc*), it is possible to determine in which groups of patients positive therapy effects are to be expected, and whether the drug efficacy depends on the patients' age at therapy onset or on osteoporotic bone fracture in their history or base DXA results or base values of bone metabolism marker concentrations.

The following information draws on *post hoc* analyses of the above-mentioned main clinical studies (STRATOS, SOTI, TROPOS).

Influence of patients' age prior to treatment

Strontium ranelate effectively prevents spinal fractures in post-menopausal women regardless of their age.

Strontium ranelate was found to be the first anti-osteoporotic agent of long-term efficacy in preventing vertebral and nonvertebral fractures during five-year therapy in women aged > 80 years [16]. Vertebral fracture risk was reduced by 31% and nonvertebral fracture risk by 27% in patients aged > 80 years during five years of treatment [16].

The three-year treatment with strontium ranelate of 1,488 women aged 80–100 decreased the risk for spinal fractures by 32%, nonvertebral fractures by 31%, and for all clinically evident fractures (vertebral and extravertebral) by 22% [18]. After one year of treatment, the risk for spinal fractures decreased by 59%, for nonvertebral fractures by 41%, and for all clinically evident fractures by 37%.

In a group of 353 women aged 50–65 with advanced post-menopausal osteoporosis (at least one vertebral fracture in their history), a four-year therapy with strontium ranelate reduced the risk of new vertebral fracture by 35% [19]. In that group, a significant increase in bone mineral density was achieved, amounting to 15.8% in the lumbar spine and 7.1% in the femoral neck.

Influence of bone mineral density prior to treatment

Strontium ranelate effectively prevents spinal fractures regardless of base bone mineral density values.

Strontium ranelate, administered for five years to 5,091 post-menopausal women with osteoporosis, decreased the risk of vertebral fractures by 24% and of nonvertebral fractures by 15% vs. the placebo group. The risk of hip fractures in a group of 1,128 women

(a *post hoc* analysis in a group of women at high risk of bone fracture i.e. ≥ 74 years and with lumbar spine and femoral neck DXA T-score ≤ –2.4) decreased during five years of treatment by 43% vs. the placebo group [20].

Strontium ranelate, administered in a group of women with lumbar spine osteopenia and any femoral neck DXA score, reduced the risk of spinal fracture in women with or without vertebral fracture in their history [21].

Effect of bone fracture in history prior to treatment

An analysis of results from the SOTI and TROPOS programmes [22], concerning women aged > 74, found that the anti-fracture efficacy of strontium ranelate in the spine did not depend on spinal fracture(s) in history before therapy onset.

Effect of the concentration of bone metabolism markers prior to treatment

No difference has been demonstrated between the anti-fracture efficacy of strontium ranelate in the spine vs. the base values of bone metabolism markers [23]. The three-year study, in which the activity of alkaline phosphatase bone fraction (bone formation marker) and the concentration of CTx (C-terminal, cross-linked telopeptide of collagen-I, bone resorption marker) in serum were studied, concerned women with post-menopausal osteoporosis.

Influence of other factors present prior to treatment

An analysis of results from the SOTI and TROPOS programmes [22], concerning women aged > 74, found that the anti-fracture efficacy of strontium ranelate within the spine did not depend either on osteoporosis in family history or on tobacco smoking.

In whom does strontium ranelate increase bone mineral density?

Influence of patients' age prior to treatment

A positive effect of strontium ranelate on bone mineral density was observed regardless of the age of post-menopausal women.

In older women, that effect was demonstrated in the STRATOS [7], SOTI [8] and TROPOS [9] studies.

In women in the early post-menopausal period, that effect was shown in the PREVention Of early post-menopausal bone loss by Strontium ranelate (PREVOS) study [24]. A dose of 1.0 g/day of strontium ranelate was found to be the smallest effective dose to prevent bone mass loss in women in the early post-menopausal period. After two years of treatment, a significant increase in bone mineral density was obtained in the lumbar spine and the femoral neck vs. the placebo group.

Which factors give a prognosis of the anti-fracture efficacy of strontium ranelate?

Identifying the changes observed in the course of treatment which determine the anti-fracture efficacy of strontium ranelate is very important. Since the degree to which bone mineral density changes during the applied treatment is the main index of its efficacy, it is important to determine the degree by which bone fracture risk reduction depends on bone mineral density. It is also imperative to discover whether changes in the concentration of bone metabolism markers give a prognosis of bone fracture risk reduction.

Effects of bone mineral density changes on the anti-fracture efficacy of strontium ranelate

Changes in bone mineral density may go a long way to explaining the anti-fracture efficacy of strontium ranelate in osteoporosis therapy.

Bone mineral density changes in the femoral neck and the total hip, observed after three years of treatment, were responsible for the reduction of risk of new spinal fractures by 76% and 74%, respectively [25].

The 1% increase of bone mineral density in the femoral neck after three years of therapy was associated with a decreased risk of new vertebral fractures of 3%.

The 1% increase of bone mineral density in the total hip after three years of therapy was associated with a decreased risk of vertebral fracture by 2%.

The increase of bone mineral density in the femoral neck after one year of therapy was significantly associated with a decreased risk of vertebral fractures after three years of therapy.

Changes in bone mineral density in the lumbar spine after three years of treatment were not significantly associated with a decreased risk of new vertebral fractures.

Changes in bone mineral density in all the skeleton fragments were not connected with a decreased risk of nonvertebral fractures.

Another report [10] found that bone mineral density changes in the total hip negatively correlated with the risk of vertebral fractures during the last three years of an eight-year therapy with strontium ranelate. The increase of bone mineral density in the total hip during the eight-year therapy assumed reduction of the risk of new vertebral fractures in post-menopausal osteoporosis. A 1% increase of bone mineral density in the total hip reduced the risk of vertebral fracture by 5%.

Bone metabolism changes evaluated by changes in the concentration of bone metabolism markers

Changes in the concentrations of all the studied bone metabolism markers, observed after three months of therapy, did not initially assume any efficacy of the three-year anti-fracture therapy with strontium ranelate [26].

The concentration changes of bone metabolism markers explained less than 8% of bone mineral density changes. Changes in the concentration of pro-collagen type I C-terminal peptide (PICP) and in alkaline phosphatase bone fraction activity after three months of therapy assumed changes in lumbar spine and femoral neck bone mineral density. Changes in CTx and PICP concentrations and in the activity of alkaline phosphatase bone fraction assumed total hip BMD changes.

Cost-effectiveness of post-menopausal osteoporosis therapy with strontium ranelate

Studies into the cost-effectiveness of strontium ranelate administration in the therapy of post-menopausal osteoporosis have been performed in Belgium [27, 28] and the UK [29], estimating the costs in terms of a quality-adjusted life year (QALY).

In Belgium, cost-effectiveness was evaluated of three-year therapy with strontium ranelate, applied for women aged 75 and 80 with osteoporosis identified by DXA, or with a spinal fracture in their history. The drug turned out to be cost-effective in the group of women aged 75 with densitometric criteria for osteoporosis diagnosis and for the women aged 80 with a vertebral fracture in their history vs. untreated women or those treated with risedronate. The therapy was evaluated as cost-effective also in a five-year perspective.

In the UK, therapy with strontium ranelate was estimated as cost-effective vs. no therapy at all in a group of women aged ≥ 65 with a bone fracture in their history of an osteoporotic character, confirmed by DXA results: T-score ≤ –2.5, and in a group of women of the same age with a bone fracture in their history with no known DXA results. With the declared readiness to incur annual costs for QALY in the amount of 30 thousand pond sterling, the borderline ten-year risk of bone fracture, estimated by the FRAX® method, was 16.9%, increasing to 25.7% with annual spending for QALY at the level of 20 thousand pond sterling [29].

No Polish data is available concerning the cost-effectiveness of strontium ranelate administration in the therapy of post-menopausal osteoporosis.

A comparison of strontium ranelate with other agents of proven anti-fracture activity

No reports are available which evaluate the anti-fracture efficacy of strontium ranelate in a head-to-head study vs. that of other agents.

Alendronate

During one-year therapy with strontium ranelate, a significantly higher improvement in trabecular bone and cortical tibial bone microstructures was obtained following high resolution CT evaluations vs. that after alendronate therapy (weekly dose of 70 mg) [30].

A similar incidence of venous thromboembolic episodes has been seen in both therapeutic groups and in the placebo group [31]. The incidence of thromboembolic episodes in the UK's population of female patients treated with strontium ranelate, was similar to the incidence observed in third and fourth phase studies of the drug.

Teriparatide

No significant differences have been found between either drug, regarding its effect on the histomorphometric parameters of bone formation and resorption, while the anti-fracture activity of strontium ranelate was explained by other than anabolic effects [17]. In both therapies, a similar effect was obtained on trabecular bone mineralisation surface changes. In the teriparatide-administered group, a statistically significant increase was obtained in the values of bone formation markers (PINP and alkaline phosphatase bone fraction). In the strontium ranelate- treated group, a statistically significant reduction was observed in the concentrations of bone formation (PINP) and bone resorption (CTx) markers.

Strontium ranelate applications, following the administration of other agents with anti-fracture efficacy

After bisphosphonate treatment

Strontium ranelate administration may be considered as a continuation of long-term therapy with bisphosphonates [32]. A histomorphometric bone analysis, performed after six-month therapy, revealed increased osteoid surface and higher strontium content in the bone. Following 12 months of treatment, increased bone volumes were found, with thicker bone trabeculae and a higher strontium content in the bone. There were also a higher number of osteoblasts with increased osteoid surface and volume. Low bone resorption was observed with a small number of osteoclasts.

After teriparatide treatment

In the course of a 12-month therapy with strontium ranelate, administered to women previously treated with teriparatide for 18 months, a further increase in lumbar spine BMD was obtained [33].

Drug information

The following information summarises the publications quoted in this review, as well as the characteristics of the medicinal product.

The drug is available in granulate form (2.0 g sachets), ready to prepare oral suspension.

The drug is absorbed in the digestive tract. With a single dose of the drug > 1.0 g, the absorption process is mainly passive in character. The bioavailability of strontium ranelate is 27% and it is excreted mainly through the kidneys.

Indications

— Osteoporosis treatment in women after menopause to reduce the risk of vertebral fractures.

Contraindications

— Oversensitivity to the drug
— Renal insufficiency (creatinine clearance < 30 ml/min)

Precautions

— Carefully apply to subjects with an increased risk of venous thromboembolic disease (current and in history)
— Do not use during pregnancy or breast-feeding
— Do not combine the drug with tetracyclines or chinolones
— Do not administer the drug to bedridden or postoperative patients

Indications to withdraw drug administration

The indications for drug withdrawal include the occurrence of allergic reactions. These are: oedema of the face, tongue or pharynx, impaired breathing or swallowing, skin eruption.

In cases of oversensitivity reaction, the drug should not be prescribed in future.

Dosage in the therapy of post-menopausal osteoporosis

The drug is administered in oral doses (a 2.0 g sachet daily). Bioavailability is reduced by 60–70% with combined calcium administration and during meals, therefore:

— the drug should be administered at least two hours after a meal, optimally in the evening after dinner;
— at least a two-hour interval is recommended between strontium ranelate and calcium

No dose modification is required in case of liver diseases.

Neither vitamin D nor calcium administration is obligatory; they are, however, recommended in cases of their deficit. Adverse effects which may occur in the course of treatment are presented in Table I.

Adverse effects occur most frequently during the first three months of therapy.

Also described: vomiting, abdominal pains, irritations of oral mucous membrane, bone, joint and muscle pains, allergic reactions, pruritus, urticaria or vasomotor oedema.

Table I. *Adverse effects which may occur in the course of treatment*

Tabela I. *Działania niepożądane mogące pojawić się w czasie leczenia*

Most frequent	Less common	Rare
Nausea	Venous thrombosis	Convulsive seizures
Diarrhoea	Fainting	
Loose stool	Memory loss	
Headache	Consciousness disturbances	
Dermatitis		

Single cases of the Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been described [34, 35]. This is a rare oversensitivity reaction, usually occurring three to six weeks from therapy onset, and characterised by fever, rash, eosinophilia and generalised symptoms (e.g. hepatitis or nephritis) [35]. The occurrence of DRESS syndrome is an indication for definitive discontinuation of therapy with strontium ranelate.

Single cases have been described of severe, desquamative dermatitis after treatment with strontium ranelate [36].

Analysis performed in the UK between 2004 and 2008 concerning venous thromboembolic episodes during the first year of therapy with strontium ranelate found a similar prevalence of those episodes in an age-matched group and in a group on anti-fracture medications for post-menopausal osteoporosis [37]. The prevalence of thromboembolic episodes, recorded in the population of patients treated with strontium ranelate was similar to that observed in third and fourth phase trials of the drug.

Summary

1. Strontium ranelate is a first-line medical agent in the therapy of post-menopausal osteoporosis.
2. The mechanism of action makes the drug distinct from other medical agents, as it simultaneously stimulates bone formation and inhibits bone resorption. The activity of the drug depends on various mechanisms, including the activation of calcium receptors, localised on osteoblasts and osteoclasts and on the effects on the OPG/RANKL system.
3. The drug is effective in preventing bone and hip fractures and nonvertebral fractures. The anti-fracture efficacy within the spine does not depend on the age of the patient nor on base bone mineral density

values nor on the concentrations of bone metabolism markers. The anti-fracture efficacy in the hip concerns women with post-menopausal osteoporosis and with an increased risk of bone fracture.

4. It also decreases the concentration of bone resorption markers, while increasing the concentration of bone formation markers.
5. The very broad range of conditions in which the drug demonstrates anti-fracture efficacy makes it a very attractive proposal for pharmacological management in post-menopausal osteoporosis.

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