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Direct Healthcare Professional Communication

Important new restrictions for the use of Protelos (strontium ranelate) following new data showing an increased risk of myocardial infarction

Dear Healthcare Professional,

This letter is to inform you of the restricted indications, new contraindications and warnings with Protelos (strontium ranelate).
These measures are intended to reduce the risk of cardiac adverse events which have become evident in a recent routine analysis of safety data from patients taking Protelos.
A full evaluation of the benefits and risks of Protelos in the approved indications will now be conducted by the European Medicines Agency within the next months, and any further conclusions resulting from this evaluation will be communicated as appropriate.

Summary:

- **Available data from randomised clinical trials on the cardiac safety of Protelos in the treatment of osteoporosis show an increased risk of myocardial infarction with no observed risk in mortality.**

- **The use of Protelos is now restricted to the treatment of severe osteoporosis**
  - **in postmenopausal women at high risk for fracture**
  - **in men at increased risk of fracture.**

- **Treatment should only be initiated by a physician with experience in the treatment of osteoporosis, and the decision to prescribe strontium ranelate should be based on an assessment the individual patient's overall risks.**

- **Protelos should not be used in patients with ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or a history of these conditions, nor in patients with uncontrolled hypertension.**

- **Furthermore:**
  - **Prescribers are advised to assess the patient's risk of developing cardiovascular disease before starting treatment and thereafter at regular intervals.**

- **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 with Protelos should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled.**

This letter is sent in agreement with the European Medicines Agency and Irish Medicines Board.

Further information on the safety concern:

A recent review of all available safety data for strontium ranelate, has raised concern about its cardiovascular safety beyond the already recognized risk for venous thromboembolism. An analysis of randomised controlled trial data has identified an increased risk for serious cardiac disorders, including myocardial infarction (MI) with no observed risk in mortality. This conclusion is predominantly based on data from pooled placebo-controlled studies in post-menopausal osteoporotic patients (3803 patients treated with strontium ranelate, corresponding to 11270 patient years of treatment, and 3769 patients treated with placebo, corresponding to 11250 patient years of treatment). In this data set, a significant increased risk of myocardial infarction was observed in strontium ranelate-treated patients as compared with those given placebo (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]). Further, there was an imbalance of more serious cardiac events, including myocardial infarction, associated with strontium ranelate both in a study in osteoporotic men, and in a study in osteoarthritis. In addition, there is a possible mechanistic rationale for an increased risk of serious cardiac disorders including myocardial infarction, given the thrombotic potential of strontium ranelate.

In order to minimize the risk of MI , the product information has been strengthened as detailed above, including restricted indications and introduction of contraindications and warnings and a recommendation to prescribers to base the decision to prescribe strontium ranelate on an assessment of the individual patient´s overall risks.

Call for reporting

As a reminder, there is a need to report any suspected adverse reactions to the Irish Medicines Board using a Yellow Card obtained either from the IMB, or electronically via the website at www.imb.ie. Adverse reactions can also be reported by calling on (01) 676 4971.

Company contact point

For further inquiries concerning this information, please contact the Medical Information Department of SERVIER Laboratories Ireland 01-6638110 and Medical and Regulatory Affairs Manager, Servier Laboratories, Block 2, West Pier Business Campus, Old Dunleary Road, Dun Laoghaire, Co. Dublin

Yours sincerely,

Mr Yann Mazeman PharmD

General Manager

Annex: relevant sections of the Product Information that have been revised (changes highlighted in underlined text)

4.1 Therapeutic indications

Treatment of **severe** osteoporosis in postmenopausal women **at high risk for fracture** to reduce the risk of vertebral and hip fractures (see section 5.1).
Treatment of **severe** osteoporosis in adult men at increased risk of fracture (see section 5.1).
The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).

4.2 Posology and method of administration

[...]
Treatment should only be initiated by a physician with experience in the treatment of osteoporosis.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.
Temporary or permanent immobilisation 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.

4.4 Special warnings and precautions for use

[...]
Cardiac ischaemic events
In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in PROTELOS treated patients compared to placebo (see section 4.8).
Before starting treatment and at regular intervals, patients should be evaluated with respect to cardiovascular risk.

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 (see sections 4.3 and 4.8).

Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled (see section 4.3).

4.8 Undesirable effects

[...]
In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in Protelos treated patients) as compared to placebo (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]).

Tabulated list of adverse reactions

The following adverse reactions have been reported during clinical studies and/or post marketing use with Strontium ranelate.

Adverse reactions, defined as adverse events considered at least possibly attributable to strontium ranelate treatment in phase III studies are listed below using the following convention (frequencies *versus* placebo): very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class (SOC) *FREQUENCY CATEGORY* Adverse Reaction	Percentage of Patients Experiencing the adverse reaction Treatment	
	Strontium ranelate (n=3352)	Placebo (n=3317)
Psychiatric disorders		
Frequency unknown:[a]		
Confusional state	-	-
Insomnia	-	-
Nervous system disorders		
Common:		
Headache	3.3%	2.7%
Disturbances in consciousness	2.6%	2.1%
Memory loss	2.5%	2.0%
Uncommon:		
Seizures	0.4%	0.1%
Frequency unknown:[a]		
Paraesthesia	-	-
Dizziness	-	-
Vertigo	-	-
Cardiac disorders		
Common[d]**:**		
Myocardial infarction	**1.7%**	**1.1%**
Vascular disorders		
Common:		
Venous thromboembolism (VTE)	2.7%	1.9%
Respiratory, thoracic and mediastinal disorders		
Frequency unknown:[a]		
Bronchial hyperreactivity	-	-
Gastrointestinal disorders		
Common:		
Nausea	7.1%	4.6%
Diarrhoea	7.0%	5.0%
Loose stools	1.0%	0.2%
Frequency unknown:[a]		
Vomiting	-	-
Abdominal pain	-	-
Oral mucosal irritation (stomatitis and/or mouth ulceration)	-	-

Gastrooesophageal reflux	-	-
Dyspepsia	-	-
Constipation	-	-
Flatulence	-	-
Dry mouth		
Hepatobiliary disorders		
Frequency unknown:[a]		
Serum transaminase increased (in association with hypersensitivity skin reactions)	-	-
Hepatitis	-	-
Skin and subcutaneous tissue disorders		
Common:		
Dermatitis	2.3%	2.0%
Eczema	1.8%	1.4%
Rare:		
DRESS (see section 4.4)	-	-
Very rare:		
Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis[c] (see section 4.4)		
Frequency unknown:[a]		
Hypersensitivity skin reactions (rash, pruritus, urticaria, angioedema)	-	-
Alopecia	-	-
Musculoskeletal and connective tissue disorders		
Frequency unknown:[a]		
Musculoskeletal pain (muscle spasm, myalgia, bone pain, arthralgia and pain in extremity)	-	-
General disorders and administration site conditions		
Frequency unknown:[a]		
Peripheral oedema		
Pyrexia (in association with hypersensitivity skin reactions)	-	-
Malaise	-	-
Blood and Lymphatic disorders		
Frequency unknown:[a]		
Bone marrow failure	-	-
Eosinophilia (in association with hypersensitivity skin reactions)	-	-
Lymphadenopathy (in association with hypersensitivity skin reactions)	-	-
Investigations		
Common:		
Blood Creatine phosphokinase (CPK) increased[b]	1.4%	0.6%

[a] *Post-marketing experience*

[b] *Musculo-skeletal fraction > 3 times the upper limit of the normal range. In most cases, these values spontaneously reverted to normal without change in treatment.*

[c] *In Asian countries reported as rare*

[d] ***In pooled placebo-controlled studies of post-menopausal osteoporotic patients, strontium ranelate treated patients (N=3803) compared to placebo (N=3769)***