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Filter: Submission No. PM 20010-02598-3-5

Product	**Strontium Ranelate 2 g granules for oral suspension (PROTOS)**
Sponsor	Servier Laboratories (Australia) Pty Ltd
Type of Drug	bone modulating agent
Type of application	Cat 1, Type J; application to change the PI requiring evaluation of data.

Background

Strontium ranelate (Protos) was registered for the Indication "Treatment of postmenopausal osteoporosis to reduce the risk of fracture" in June 2005. There have been several SRNs. A patient information leaflet additional to the CMI was approved in November 2008.

This submission, to update the PI in line with the EU Summary of Product Characteristics, proposes changes to the Adverse Reactions Section, with some additional minor editorial changes, and an updated CMI.

Administrative issues

The dossier consists only of Module 1, with no clinical data. The EU SPC has been provided as the reference document for the tracked changes in the proposed PI. These changes appear to accurately reflect the SPC, which has all Adverse Reactions, both from clinical trials and post-marketing, presented in one table. However the SPC is not sufficient *per se* as the source document, as it does not provide the evidence for the proposed changes.

Clinical Evaluation issues

1. The Adverse Reactions in Clinical Trials section is reformatted into CIOMs categories and updated to reflect the figures in the SPC tabulation. From the subject numbers, it appears that all these events are from the original clinical trials.
2. The Adverse Reactions Post-Marketing Experience heading has new events under additional SOCs. These events must reflect post marketing data; the TGA has two PSURs subsequent to the last review, covering 21/3/2007 to 21/9/2008.

Notes to evaluator

Please read the original CER for strontium ranelate, (Submission 2004/03945, commencing at File 2004/14527, discussed at ADEC 239th meeting 31/3/2005, Item 2.12), with respect to Adverse Events and Adverse Reactions reported in evaluated Phase III trials.
Are the proposed tabulations from the SPC consistent with the TGA evaluation of data?

Please review the PSUR data provided to the TGA, following the latest review at File 2005/043249, folios 11-18. Are the proposed SOC and event term changes to 'Post-Marketing Experience' consistent with available reports? From your evaluation, are there any other events that should be considered for inclusion in the PI?

Questions for AET S31

The SPC is not sufficient as the source document for proposed changes, because it does not provide data or specific evidence for changing the PI.

1. If the SPC clinical studies Adverse Reactions are from Phase III trial data already evaluated by the TGA, please cross reference. If not, please provide the additional data for evaluation.
2. If the additional post-marketing adverse reactions are derived from PSURs provided to the TGA, please indicate the relevant reports and analyses. If not, please provide the data for evaluation.

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Name of Drug:	Strontium Ranelate 2g granules for oral suspension (sachet)
Trade Name:	PROTOS
Sponsor:	Servier Laboratories (Australia) Pty Ltd
App No.:	2010-02598-3-5
App Type:	3 : PI changes
Formulation:	
Proposed Indication:	~~menopausal osteoporosis to reduce the risk of fracture~~". No change to existing approved indications: "Treatment of post-menopausal osteoporosis to reduce the risk of fracture"
Proposed Dosage:	

Purpose of Present Application

Update to Product Information to align safety information in the Australian approved Protos PI with the recently revised Reference Safety Information - variation

Overview of the Dossier in CTD format N/A

Module 1 Vol: 1	2 copies, 100 pages
Module 2 Vol:	N/A
Module 3 Vol:	N/A
Module 4 Vol:	N/A
Module 5 Vol:	1 → 30 pages (= Module 1 volume)

Module 1 & 2 Overview

Literature Based Submission:	N/A
Application form indication matches PI and app letter:	Yes
PI: Registered: (all strengths and sizes)	Module 1.3.1 p 35-57
PI: ~~Marketed~~: Proposed (Tabled changes	
CMI:	Module 1.3.2 p58-67:
SPC / Core Data Sheet: (Reference Safety Information)	Module 1.10 p83-113 : Date of Revision not stated
CD-ROM:	N/A
Labels:	No changes proposed
PAR (should be provided) or details in app form:	No changes proposed ✓ Mod 1
Confidentiality statement:	N/A.
Data Protection from other drugs affect this application:	N/A
GTR product and referral to OGTR needed:	N/A
International Regulatory Status:	Approved in EU 26/8/2010
Rejection Statement for USA and Canada:	"Not registered in USA or Canada"
Ethics Declaration (module 2/5):	No clinical data provided
Human Embryo and Stem Cell declaration	N/A
IPD Statement:	N/A
Paediatric data or justification:	N/A
GMP certificates or pre-clearances submitted:	N/A
GCP statement (module 2/5):	No clinical data provided
Bio data or justification:	N/A
Environmental Risk Assessment for GMO or non-GMO:	N/A
Information on Experts and signed declaration	N/A - no expert reports
Formulation in CT same as registration:	No clinical data provided
References for Clinical Reports / Summaries provided:	SmPC only
References in English and legible:	SmPC only

Module 5

No Module 5 data provided

Number Changes are based on 'alignment' to EU SmPC, to present AEs from Clinical Trials (already evaluated, judging from patient numbers cited - currently approved PI text) & CIOMS forms

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... types of studies:	(1) Significant differences in classified events from the currently approved PI, also (2) ? Inconsistencies in VTE: current PI has annual incidence, cf. new text ? yr 0 – 5 of previous table (3) Additional SOCs = post-marketing experience
(4) Is CMI c/w proposed PI?	
Regulatory Issues	
Class statements, Minutes from ADEC/ADRAC, Overseas evaluations or Previous evaluations relevant:	(1) (ADEC) ACPM Minutes 239th Meeting 31/3-1/4/2005 Item 2.12 PROTOS (2) CER for registration of PROTOS, Submission 2004/03945, commenting on Clin File 2004/14527. (Not attached to PREMIER)
PI changes to indications or dosage without supporting data:	No changes to Indications or Dosage proposed
Resubmission and have the reasons for previous withdrawal or rejection been addressed:	N/A
Guidelines for this drug (eg EU, LBS, External):	
(3) PSURs –08-0184-03-08 –08-0424-09-08	(4) PI/CMI 2005/04324?
Conclusion	
Discussed with Section Head:	yes
Decision (Accept, S31, Reject):	S31 to request location or provision of data for evaluation
Indication for this unit:	Yes (osteoporosis)
Application added to spreadsheet:	
Red Folder signed:	
Premier completed:	
Issues	
• ARs in Clin-trials ? all previously evaluated data? see CER 2004/03945	
• ARs for Post-Marketing – ? derived from non-reviewed PSURs, or subsequent PSURs not yet provided?	

→ Request clarification, and additional data from Sponsor if necessary.

Clinical Evaluation Unit 5
Office of Prescription Medicines 14/9/2010