Parareg

Procedural steps taken and scientific information after the authorisation

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0015	Update of the Detailed Description of the Pharmacovigilance system (DDPS) version 3.0.	25/09/2008	29/10/2008	Annex II	The MAH updated the Detailed Description of the Pharmacovigilance system (DDPS) with administrative changes to provide further clarity.
II/0011	Extension of Indication Addition of a new indication for reduction of hypercalcaemia in patients with primary hyperparathyroidism (HPT), for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated. The Package Leaflet has been updated further to the results of the readability testing. The list of local representatives has been updated. In addition, the MAH has submitted the Pharmacovigilance System (version 2.1) and an updated Risk Management Plan (version 1.0). Annex II has been updated to reflect this update.	24/04/2008	18/06/2008	SPC, Annex II, PL	Please refer to the scientific discussion Parareg – H-C-570-II-11 Scientific Discussion
II/0012	Update section 4.4 of the SPC to reflect data from the Study 20020158 regarding testosterone levels, as requested by the CHMP.	21/02/2008	17/03/2008	SPC	Update to section 4.4 of the Summary of Product Characteristics (SPC) with the results of the Study 20020158, showing no further reductions in free and total testosterone concentrations over a period of 3 years in cinacalcet-treated patients.

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet)

II/0010	Update of the section 4.5 of the Summary of Product Characteristics to reflect the data from the study 20050226 using midazolam, demonstrating that the co-administration of cinacalcet would not alter the pharmacokinetics of classes of drugs metabolised by CYP3A4 and CYP3A5 enzymes.	15/11/2007	21/12/2007	SPC	The study 20050226 was a randomized, single center, open-label, 2-period, 2-treatment, 2-sequence, crossover study in healthy volunteers. The results show no effect of cinacalcet on midazolam plasma concentrations indicating low inhibitory potential of cinacalcet on CYP3A4/5. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of drugs that are metabolized by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.
II/0009	Update of safety information following observations from post-marketing surveillance to include hypotension and/or worsening of heart failure, in sections 4.4 and 4.8 of the SPC, as well as diarrhoea in sections 4.8 in line with the recently revised Core Data Sheet. The section 4 of the Package Leaflet has been updated to reflect these changes. The contact details of the local representatives of Bulgaria and Romania have also been inserted. The Latvian local representative contact details have been amended. Minor editorial corrections are inserted in Labelling.	19/07/2007	31/08/2007	SPC, Labelling, PL	The MAH has submitted this variation application to update the SPC and the PL with post-marketing information and post-hoc analysis of clinical trials regarding cases of hypotension and/or worsening of heart failure in patients. In addition diarrhoea has been added to section 4.8 of the SPC and in the relative section of the PL. The contact details of the local representatives of Bulgaria and Romania have also been inserted. Minor editorial corrections are inserted in Labelling.
II/0008	Update of the Summary of Product Characteristics (SPC), sections 4.4 and 5.1, to reflect Safety data from the final analysis of Study 20000178, assessing the safety and efficacy of cinacalcet in patients with chronic kidney disease (CKD) with secondary hygerparathyroidism, not on dialysis (CKD stage 3 and 4 population).	19/07/2007	31/08/2007	SPC	The MAH submitted the Study 20000178 in patients with secondary HPT and CKD not receiving dialysis. The efficacy results of this study were presented and they were in principle consistent with those previously submitted. Even if the current study was modified to reduce the incidence of hypocalcaemia, the incidence of low serum calcium concentrations remained in principle similar with that observed in previous studies. The events of hypocalcemia were predominantly asymptomatic laboratory findings without discernible clinical sequelae. Consequently section 4.4 of the SPC was updated to include the warning for hypocalcaemia in patients not on dialysis compared with cinacalcet-treated CKD patients on dialysis. Section 5.1 of the SPC has been updated as well to include the information derived from the study 20000178 in patients with CKD and secondary HPT not undergoing dialysis.

II/0007	The Marketing Authorisation Holder applied for an update of section 5.3 of the Summary of Product Characteristics to include information on surrounding activity on secondary receptors, following CHMP recommendation.	01/06/2006	13/07/2006	SPC	The MAH has performed additional non-clinical studies investigating the activity on the primary receptor (CaR) and the two secondary receptors as requested by the CHMP at the time of the granting of the initial marketing authorisation. In in vitro studies, IC50 values for the serotonin transporter and KATP channels were found to be 7 and 12 fold greater, respectively, than the EC50 for the calcium-sensing receptor obtained under the same experimental conditions. The clinical relevance is unknown, however, the potential for cinacalcet to act on these secondary targets cannot be fully excluded This new data have been included in section 5.3 of the SPC.

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IB/0014	12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening		29/07/2008
IA/0013	13_a_Change in test proc. for active substance - minor change		13/02/2008
IB/0006	42_a_01_Change in shelf-life of finished product - as packaged for sale	SPC	19/04/2006
IB/0001	42_a_01_Change in shelf-life of finished product - as packaged for sale	SPC	02/02/2005
IA/0002	04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)		27/01/2005

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change