EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Osseor

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision issued [2] / amended on	Product Information affected [3]	Summary
SW/0045	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0013	22/03/2018	22/05/2018	SmPC, Annex II and PL	The PASS final study report submitted by the MAH complies with their obligation to perform a PASS to evaluate risk of serious cardiac disorders as imposed during the Article 20 procedure EMA/112925/2014. Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorization were warranted.
PSUSA/9301/	Periodic Safety Update EU Single assessment -	17/05/2018	n/a		PRAC Recommendation - maintenance

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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201709	strontium ranelate				
II/0042	Update of section 4.4 of the SmPC in order to update the safety information regarding hypersensitivity reactions in Asian patients based on the results of a pharmacogenetics, retrospective, case-control study conducted in Singapore with Singapore Immunology Network (SIgN). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	11/09/2017	SmPC, Annex II, Labelling and PL	HLA-A*33:03 and HLA-B*58:01 alleles have been identified as potential genetic risk factors for strontium ranelate-associated SJS/TEN in Han Chinese patients from a retrospective, case-control, pharmacogenetic study. Where possible, screening for HLA-A*33:03 and HLA-B*58:01 alleles could be considered before starting treatment with OSSEOR in patients of Han Chinese origin. If tests are positive for one or both alleles, OSSEOR should not be started. However, absence of these alleles upon genotyping does not exclude that SJS/TEN can still occur.
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2015	11/09/2017	PL	
PSUSA/9301/ 201409	Periodic Safety Update EU Single assessment - strontium ranelate	10/04/2015	n/a		PRAC Recommendation - maintenance
IAIN/0040/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	18/02/2015	n/a		

	manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
II/0038	Submission of a revised RMP version 14, as requested by CHMP, to include the measures agreed during the recent article 20 procedure. The requested variation proposed no amendments to the PI. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	26/06/2014	n/a		
PSUV/0037	Periodic Safety Update	25/04/2014	19/06/2014	SmPC and PL	For further information please refer to: Osseor-H-561-Grounds-PSUV-37-en.
R/0036	Renewal of the marketing authorisation.	20/03/2014	22/05/2014	SmPC, Annex II and PL	The benefit/risk balance of Protelos/Osseor has been thoroughly assessed by the PRAC and the CHMP within a recent Art.20 referral procedure. At its February 2014 meeting, the CHMP adopted an opinion where the Marketing Authorisation is maintained, subject to changes of the product information and to the RMP. The PRAC and CHMP are of the view that no new data have been provided since the outcome of the benefit risk assessment for Protelos/Osseor in February 2014 that would have an impact on the overall benefit/risk balance of the product. Therefore, the overall benefit risk balance for

					Protelos/Osseor remains positive in the restricted population as recommended by the CHMP in February 2014 and there are no objections against the renewal of the Marketing Authorisation from the PRAC or CHMP. The product information was updated in line with the latest QRD template.
A20/0034	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 25 April 2013 the recommendation of the PRAC further to a wide-ranging evaluation of the benefits and risks of Protelos and Osseor following the identification of a risk of serious cardiac disorders including myocardial infarction and the already recognised safety concerns such as serious skin disorders and venous thrombotic events (VTE). The PRAC was requested to assess the impact thereof on the benefit-risk- balance of Protelos and Osseor and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn. The notification for the procedure is appended to this recommendation.	20/02/2014	15/04/2014	SmPC, Annex II and PL	Please refer to the CHMP scientific conclusions and PRAC assessment report: Osseor EMEA/H/A20/1371/C/000561/0034.
IB/0035	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2013	15/04/2014	SmPC and PL	
IAIN/0033	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/11/2012	n/a		
II/0032	Update of section 4.4 of the SmPC to include further	20/09/2012	23/10/2012	SmPC, Annex	The MAH has undertaken an evaluation of safety signals,

	safety information in order to highlight the more frequent occurrence of severe skin hypersensitivity reactions in patients of Asian origin, and update of section 4.8 of the SmPC to add the ADRs 'parasthesia', 'dry mouth', 'vertigo', 'dizziness' and 'malaise' reported post-marketing. The Package Leaflet has been updated in accordance. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 8, rev 1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II, Labelling and PL	taking into account all adverse drug reactions for Protelos/Osseor reported from 22 December 2011 to 21 March 2012. Based on a following cumulative data analysis of all safety data generated from authorisation on 21 September 2004 to 21 March 2012, the MAH proposed to update section 4.8 of the SmPC to add the ADRs 'parasthesia', 'dry mouth', 'vertigo', 'dizziness' and 'malaise' reported post-marketing. Fifty-nine (59) cases of dry mouth were reported cumulatively from marketing authorisation until the DLP (4 events considered as serious). Twenty-eight (28) cases were medically confirmed. Among these 59 cases, the event regression seemed linked to drug withdrawal (positive dechallenge) in 21 cases. Four (4) cases of dechallenge and rechallenge positive were reported. One hundred and twenty-nine (129) events of paraesthesia (including dysaesthesia, hypoaesthesia, paraesthesia, formication, skin burning sensation and burning sensation) were reported in 121 patients cumulatively from marketing authorisation until the DLP (26 events considered as serious). Among the 129 events, the regression seemed linked to drug withdrawal for 52 events (positive dechallenge). Eleven (11) cases of dechallenge and rechallenge positive were reported. One hundred and fifty-three (153) cases of dizziness were reported cumulatively from marketing authorisation until the DLP (30 events considered as serious). Eighty-eight (88) cases were medically confirmed. Among these 153 cases, the event regression seemed linked to drug withdrawal (positive dechallenge) in 79 cases. Eleven (11) cases of dechallenge and rechallenge positive were reported. Fifty-eight (58) cases of vertigo were reported cumulatively

					from marketing authorisation until the DLP (10 events considered as serious). Thirty-five (35) cases were medically confirmed. Among these 58 cases, the event regression seemed linked to drug withdrawal (positive dechallenge) in 29 cases, including 1 case for which an alternate (non drug) explanation has been excluded after appropriate search (possible semiology). Two (2) cases of dechallenge and rechallenge positive were reported. One hundred and twenty-one (121) cases of malaise were reported cumulatively from marketing authorisation until the DLP (28 events considered as serious). Seventy-two (72) cases were medically confirmed. Among these 121 cases, the event regression seemed linked to drug withdrawal (positive dechallenge) in 68 cases. Eight (8) cases of dechallenge and rechallenge positive were reported. In addition, the MAH proposed to update section 4.4 of the SmPC to include a statement on possible higher incidence, although still rare, of severe hypersensitivity reactions including skin rash, Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) in patients of Asian origin. An independent Expert Committee (EC) has been established in order to review and assess all cases of hypersensitivity skin reactions in patients treated with strontium ranelate. The associated risk minimisation activities are already summarised in the latest RMP assessed by the CHMP (version 11 dated May 2012). A higher occurrence of severe skin hypersensitivity reactions such as Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) was observed in Asians as compared to non-Asians in the cumulative analysis. In a cumulative EC review from 21 September 2004 to 21 March 2012 there were 9 cases of SJS and TEN in Asian countries (Asian global incidence: 1/ 7,646

					PY) vs 6 in non-Asian countries (Non-Asian case incidence: 1/ 481,661 PY). The outcome was fatal in 2 cases and reported as not recovered in one case. Following the assessment of the data provided, the CHMP agreed that the amendments proposed to sections 4.4 and 4.8 of the SmPC are adequately supported by the overall safety data presented by the MAH. All five adverse effects proposed to be introduced into section 4.8 of the SmPC as adverse events are adequately supported by data from the MAH's evaluation of safety reports received. Hypersensitivity syndrome is an identified well-known adverse event associated with strontium ranelate. These cases were assessed in depth by the CHMP as part of a recent article 20 procedure and section 4.4 of the SmPC was revised as an outcome to provide more detailed information in this regard. However, the issue of a different incidence of severe hypersensitivity reactions in Asians as compared to non-Asians was not discussed as part of the referral procedure. Based on the safety data provided, it can be concluded that the Asian global incidence is considerably higher than the incidence of cases in the Non-Asian population. However, it should be highlighted that the number of cases overall is very low. The issue of a possible relationship between the higher incidence of SJS-TEN reported in Asian populations with the use of strontium ranelate and a possible genetic susceptibility has been raised. In this regard, the search for pharmacogenomic risk factors such as HLA screening is already part of the latest approved RMP for strontium ranelate. In conclusion, the CHMP considered the amended PI acceptable and agreed that the safety data presented do not alter the positive

					benefit-risk balance for the product at this point in time.
II/0027	Extension of indication to include 'treatment of osteoporosis in men at increased risk of fracture'. Consequently, sections 4.1, 4.6, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, upon request by the CHMP, Annex II has been updated to reflect the fact that the MAH should provide 6-monthly PSURs unless otherwise specified by the Committee. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/05/2012	27/06/2012	SmPC, Annex II and PL	For further information please refer to the scientific discussion: Osseor-H-C-561-II-27-AR.
A20/0030	Article 20 review Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the CHMP to assess the safety concerns of venous thromboembolism and serious skin reactions and its impact on the benefit-risk balance of strontium ranelate. The European Commission requested the CHMP to give its opinion as to whether measures are necessary to ensure the safe and effective use of strontium ranelate, and specifically whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.	15/03/2012	25/05/2012	SmPC, Annex II and PL	For further information please refer to the scientific discussion: Osseor-H-C-561-A-20-0030-AR.
IA/0029	A.1 - Administrative change - Change in the name	28/10/2011	25/05/2012	SmPC, Annex	

	and/or address of the MAH			II, Labelling and PL	
II/0028	Update of Summary of Product Characteristics and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	18/08/2011	SmPC and PL	Update of section 4.8 of the SmPC, to add the ADRs 'gastrooesophageal reflux', 'dyspepsia', 'constipation', 'hepatitis', 'insomnia' and 'flatulence' based on post-marketing experience. Section 4 of the Package Leaflet has been updated accordingly.
II/0026	Update of Summary of Product Characteristics and Package Leaflet C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/01/2011	28/02/2011	SmPC and PL	Update of section 4.8 of the SPC with the addition of the ADR 'bone marrow failure' upon request by the CHMP following the assessment of PSUR 10. In addition, the MAH took the opportunity to add the ADRs 'eosinophilia' and 'lymphadenopathy' to section 4.8 of the SPC based on post-marketing experience. The Package Leaflet has been updated accordingly. The MAH presented a cumulative review of cytopenic disorders as part of the 10th PSUR. Since the start of marketing, there were a total of 46 case reports (53 events) corresponding to cytopenic blood disorders collected from the SOC Blood and lymphatic disorders and from the SOC Investigations. Among the cases presented by the MAH, there were cases of blood cytopenic disorders (some in association with skin reactions) with a suspected causal relationship to Osseor. Furthermore, 63 cases of eosinophilia and 25 cases of lymphadenopathy have been reported cumulatively. As part of this variation application, the MAH has presented a summary of the individual cases with information on time to onset, relevant medical history and outcome. Most of the

					cases occurred within the first months of treatment and was part of a hypersensitivity reaction. The proposed changes to the SPC and Package Leaflet (see above) can be endorsed. The benefit/ risk balance for Osseor remains unchanged.
IA/0025	Addition of an alternative secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/11/2010	n/a		
II/0024	Update of section 4.8 of the SPC upon request by the CHMP following the assessment of PSUR 9 to add the ADR 'alopecia' (frequence unknown). The Package Leaflet has been updated accordingly. In addition, the annexes have been revised in line with the latest QRD template. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	22/07/2010	26/08/2010	SmPC, Annex II and PL	Update of section 4.8 of the SPC upon request by the CHMP following the assessment of PSUR 9 to add the ADR 'alopecia' (frequence unknown). The Package Leaflet has been updated accordingly. In addition, the annexes have been revised in line with the latest QRD template.
IA/0023	B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	19/04/2010	n/a		
II/0022	Update of Summary of Product Characteristics and	19/11/2009	08/01/2010	SmPC and PL	Further to a review of cases of transaminases increased or

	Package Leaflet. To update section 4.8 of the SPC in order to include the adverse reactions elevated liver enzymes (serum transaminases) and pyrexia observed in the context of skin hypersensitivity reactions as requested by the CHMP further to the assessment of the Renewal. Section 4 of the PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				abnormal hepatic enzymes and pyrexia during the Renewal of Osseor, the MAH was requested to amend section 4.8 "Undesirable effects" of the SPC with information from post marketing reports of elevated liver enzymes and pyrexia (observed in the context of skin hypersensitivity reactions). A total of 17 cases of pyrexia and 13 cases of elevated transaminases following the use of Strontium ranelate were reviewed. Based on this assessment, the CHMP agreed on the update of the SPC to include the terms pyrexia under the MedDRA System Organ Class (SOC) "General disorders and administration site conditions" and elevated liver enzymes under "Hepatobiliary disorders". Both adverse reactions were included with the statement "frequency unknown", as no information on the frequency could be derived from clinical studies. The PL was updated accordingly.
R/0020	Renewal of the marketing authorisation.	23/07/2009	04/11/2009	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Osseor remains positive, but considers that its safety profile is to be closely monitored for the following reasons: The adverse events reported for Osseor such as venous thromboembolism, central nervous system events, creatine kinase increase including cases with rhabdomyolysis, hypersensitivity skin reactions, blood disorders, pancreatitis, photosensitivity, alopecia and hepatobiliary disorders require review and continuous monitoring and assessment in the next PSURs. Considering the safety profile of Osseor and the large number of patients currently enrolled in clinical and post

					marketing studies for the product as well as the continued reports of adverse events received by the MAH, the safety profile will continue to be monitored closely and updates should be provided regularly to the CHMP through 6-monthly PSURs. Therefore, based on the above presented Pharmacovigilance grounds, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0021	To update section 4.8 of the SPC to include the adverse events bronchial hyperreactivity and toxic epidermal necrolysis as requested by CHMP further to the assessment of the 7th PSUR. Section 4 of the package leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	28/07/2009	SmPC and PL	Following a cumulative review of cases concerning asthma and dyspnoea and two cases of Toxic Epidermal Necrolysis (TEN) in PSUR 7 (covering the period 22.03.2008 - 21.09.2008), the MAH was requested to update section 4.8 of the SPC. A total of 9 cases of asthma and 27 cases of dyspnoea following the use of Osseor were reviewed. Based on this review the CHMP agreed on the update of the SPC to include the term bronchial hyperreactivity under the MedDRA System Organ Class (SOC) "Respiratory, thoracic and mediastinal disorders", and the term toxic epidermal necrolysis under the SOC "Skin and subcutaneous tissue disorders". Both adverse events were included with the statement "frequency unknown", as no information on the frequency could be derived from clinical studies. The PL was updated accordingly.
II/0019	Update of Summary of Product Characteristics and Package Leaflet to update section 4.8 of the SPC to include the adverse events peripheral oedema and confusional state as requested by CHMP further to the assessment of the 6th PSUR, period covered 22 March 2007 to 21 March 2008. Section 4 of the package leaflet is updated accordingly.	22/01/2009	09/03/2009	SmPC and PL	Cumulatively, since start of marketing until March 2008, 24 reports of peripheral oedema and 21 reports of confusional state have been reported post marketing. In the majority of cases peripheral oedema or confusional state occurred in temporal relation to the initiation of therapy with strontium ranelate. In the majority of cases of both events an improvement was observed when strontium ranelate was

	The MAH also takes the opportunity to amend information in the list of local representatives in the package leaflet for Malta, Cyprus, Latvia and United Kingdom. Update of Summary of Product Characteristics and Package Leaflet				stopped and in some cases a positive rechallenge has been reported. The SPC and PL were therefore updated to include these two adverse events.
IA/0018	IA_09_Deletion of manufacturing site	21/11/2008	n/a		
IA/0017	IA_09_Deletion of manufacturing site	23/10/2008	n/a		
IA/0016	IA_09_Deletion of manufacturing site	23/10/2008	n/a		
IA/0015	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	18/04/2008	n/a		
IA/0014	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	18/04/2008	n/a		
IA/0013	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/03/2008	n/a		
IA/0012	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/03/2008	n/a		
IA/0011	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/03/2008	n/a		
IA/0010	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/03/2008	n/a		

II/0009	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.4 and 4.8 of the SPC to include Stevens-Johnson syndrome, severe hypersensitivity syndromes including drug rash with eosinophilia and systemic symptoms (DRESS), musculoskeletal pain including muscle spasm, myalgia, bone pain, arthralgia and pain in extremity provisionally introduced through an Urgent Safety Restriction procedure on DRESS syndrome and the CHMP assessment of the fifth PSUR for strontium ranelate. The PL is updated accordingly. The MAH also took the opportunity to update the Product Information according to the latest QRD templates and to update the list of local representatives for Bulgaria, Malta, Romania and Sweden in the Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	13/12/2007	25/01/2008	SmPC, Labelling and PL	Further to the assessment of data from the 5th PSUR and following an urgent safety restriction procedure, the CHMP considered the inclusion of DRESS syndrome and Stevens-Johnson Syndrome in the PI was considered necessary due to 16 spontaneously reported cases, of which 2 were fatal. Concerning musculoskeletal pain, the CHMP agreed on the inclusion of this adverse event due to the available data from post-marketing spontaneous reporting. The adverse reactions above are now reflected in the Product Information and are followed up adequately.
IB/0008	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	07/11/2007	n/a		
IB/0007	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	07/11/2007	n/a		

IB/0006	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	07/11/2007	n/a		
II/0005	Update of sections 4.4 and 4.8 of the SPC to introduce a statement concerning serious allergic reactions, to include new adverse events and to update the frequencies of known adverse events, as requested by the CHMP. This follows both the assessment of PSUR 3 (covering the period from 22 September 2005 to 21 March 2006) and FUM 003 (on long-term extensions of SOTI and TROPOS studies). The PL was updated accordingly. Furthermore, the MAH took the opportunity to update the Product Information according to the latest QRD template and to include the local representatives for the two new EU Member States (Bulgaria and Romania). In addition, the contact details for the local representatives of Austria, Estonia, Germany, Iceland, Ireland, Italy, Lithuania, The Netherlands, Poland, Slovenia, Slovakia and Sweden were also updated. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	28/02/2007	SmPC, Annex II, Labelling and PL	The approval of strontium ranelate in September 2004 was based on 36 months data from two ongoing 5 years clinical trials, SOTI and TROPOS. As these two trials were completed in 2006, an updated overall safety assessment based on the final 5-year study reports was submitted as a follow-up measure. It showed that the profile of adverse drug reactions observed with strontium ranelate has remained consistent with the information initially mentioned in the SPC. However, there was a need to include the updated frequencies of the mentioned adverse events. Furthermore, following the assessment of the 3rd Periodic Safety Update Report (covering the period from 22 September 2005 to 21 March 2006), the following very rare undesirable effects (reported in less than 1 in every 10,000 patients) have been added to the product information: vomiting, abdominal pain, oral mucosal irritation including stomatitis and/or mouth ulceration, hypersensitivity reactions including rash, pruritus, urticaria, angioedema. In addition, a recommendation to stop treatment in case of serious allergic reaction has been included.
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2006	n/a	PL	
IA/0003	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	24/05/2006	n/a		
IB/0002	IB_17_a_Change in re-test period of the active substance	01/04/2005	n/a		

N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/03/2005	n/a	PL	