EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Onsenal

Procedural steps taken and scientific information after the authorisation

Changes made after 1 May 2004

For procedures finalised before 1 May 2004, please refer to 'Procedural steps taken until cut-off date'.

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
II/0028	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.2 of the SmPC to include patients carrier of the CYP2C9*3 genotype in the existing recommendation on patients with suspected poor metabolism (CYP2C9 genotype carrier). Section 4.5 is updated in relation to concomitant	24/06/2010	28/07/2010	SPC, Annex II, PL	Literature review of clinical PK studies with celecoxib suggests that reduced CYP2C9 activity in patients with one or two *3 alleles may result in reduced celecoxib clearance. This evidence is sparse representing a total of 8 subjects with *3/*3 genotype in four clinical PK studies, with no more than 3 such subjects in any single study. Subjects with the *3/*3 genotype may have increased celecoxib exposures compared to *1/*1 subjects, the difference is not precisely estimated and ranges from 1 to 7 fold. Data for

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	use of celecoxib with other potent inhibitors of CYP2C9. In addition the MAH took the opportunity to update section 4.8 to add pulmonary embolism and chest pain to bring the SmPC in line with the MAH core safety information. In section 4.8, the MAH also made minor wording changes to the system organ class to bring it in line with the MedDRA System. The package leaflet is updated accordingly. In addition the MAH took the opportunity to make minor editorial changes in the Annex II and PL.				subjects with *3 heterozygous genotypes, representing a total of 16 subjects with *1/*3 or *2/*3 genotype, with no more than 7 such subjects in any single study, show smaller PK differences compared to *1/*1 subjects. Therefore, patients with the CYP2C9*3 allele, and, in particular those with CYP2C9*3*3 homozygous genotype may be exposed to celecoxib levels that are higher than those for which safety has been studied in clinical trials. The risk for high celecoxib exposure in poor metabolizers should be considered carefully when treating FAP patients. The data do not support specific dosing recommendations in patients with the CYP2C9*3 or CYP2C9*3*3 allele when treated with celecoxib 800 mg daily. Nevertheless, starting treatment at a reduced dose in these patients should be considered. There is no evidence from clinical PK studies demonstrating increased exposure to celecoxib during concomitant treatment with CYP2C9 inhibitors other than fluconazole. Nevertheless there may be potential for such increased exposure with the CYP2C9 inhibitor amiodarone. Amiodarone is added as an example of concomitant treatment that could lead in further increases in celecoxib exposure in individuals who are CYP2C9 poor metabolizers. A cumulative review of the adverse events "chest

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					pain" showed a temporal association between celecoxib initiation and onset of event and several positive dechallenge/rechallenge cases. Therefore association between celecoxib treatment and chest pain cannot be excluded. This event is added to the SmPC with a frequency category of unknown. Pulmonary embolism reported in post-marketing setting should be anticipated based on the existing warning in section 4.4 on cardio-vascular disorder nevertheless for clarification and completeness of the information this event is added to the SmPC with a frequency category of unknown.
S/0029	Annual reassessment Seventh annual reassessment of Onsenal, as the approval was granted under exceptional circumstances. The MAH took the opportunity to update annex II in line with the last QRD template.	18/03/2010	17/06/2010	Annex II	On the basis of the data submitted since the Marketing Authorisation, the benefit/risk balance in the reduction of the number of adenomatous intestinal polyps in familial polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance, remains positive. The CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances. The CHMP agreed to maintain the specific obligation for the MAH in order to generate further efficacy and safety data by undertaking a Phase III placebo-controlled trial with celecoxib in genotype positive subjects with familial adenomatous polyposis

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					(A3191193 - CHIP trial). The CHMP agreed to the amendments of the protocol in order to accelerate the recruitment rate and increase the population in the trial. The results from the CHIP trial reported so far do not allow drawing conclusive findings as the number of subjects is small and the data are preliminary. The number of polyps observed at the year-1 visit colonoscopy does not suggest that celecoxib is impacting negatively the disease progression as most subjects examined had fewer polyps than observed at baseline. The CHMP acknowledges that the small number of patients undergoing endoscopic surveillance at the time of this first progress report is limiting the analysis. In the context of the first interim analysis, foreseen at the cut- off of 30 events, the MAH is required to provide a clearer presentation of the data together with an extensive discussion of the results. The presented safety data from the CHIP trial appears to support the continuation of the trial at the planned dose. Adverse events were of mild or moderate severity and resolved. The CHMP also agreed to the draft protocol setting a three-year active surveillance program. This non-interventional study was requested by the CHMP in the frame of the 6th annual reassessment in order to generate additional safety data regarding the

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					cardiovascular risk, severe skin reactions and serious gastro-intestinal disorders should any of these occur in FAP patients treated with celecoxib. The program consists of worldwide participating sites filling out an online questionnaire on regular basis regarding adverse events associated with celecoxib treatment in FAP patients. The survey instrument is designed to capture information regarding both: Onsenal use in its authorised indication and the "off-label" use of celecoxib at any dose/duration in FAP patients.
IA/0030/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the active substance - Minor change in the manufacturing process of the active substance, B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	27/04/2010	n/a		

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S/0026	Annual reassessment Sixth annual reassessment of Onsenal, as the approval was granted under exceptional circumstances.	25/06/2009	14/10/2009	Annex II	On the basis of the data submitted since the Marketing Authorisation, the benefit/risk balance in the reduction of the number of Adenomatous intestinal polyps in familial polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance, remains positive. In order to generate further efficacy and safety data, the CHMP agreed to amend the specific obligation to include feasibility for the protocol amendment of the Phase III placebo–controlled trial with celecoxib in genotype positive subjects with familial adenomatous polyposis (A3191193 – CHIP trial). By this, it is expected that the recruitment rate of this trial will be accelerated in order to generate relevant clinical data on this orphan designation.
IB/0027	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	03/09/2009	n/a		
II/0025	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet. To harmonise the Summary of Product Characteristics (SPC) of	22/01/2009	17/03/2009	SPC, PL	Sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SPC of Onsenal were updated to include data on poor metabolizers and in lactating mothers, hypertension and renal effects, post marketing safety data and final results from the Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC), the Prevention of Colorectal Sporadic Adenomatous Polyps

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	Onsenal with the SPC of Celebra (version date 14 November 2007) as requested by the CHMP at the time of the opinion on the 4th Annual Re-assessment, with amendment to the sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SPC. The Package Leaflet was amended accordingly.				(Pre SAP) and the Alzheimer's disease Anti-Inflammatory Prevention (ADAPT) trials. In addition, a specific paragraph for skin reactions was implemented and a warning for cardiovascular risk was added.
R/0021	Renewal of the marketing authorisation	24/07/2008	20/10/2008	Annex II	
IA/0023	09_Deletion of manufacturing site	19/06/2008	n/a	Annex II, PL	
IA/0024	05_Change in the name and/or address of a manufacturer of the finished product	19/06/2008	n/a	Annex II, PL	
S/0020	Annual reassessment Fourth annual reassessment of Onsenal, as the approval was granted under exceptional circumstances.	19/03/2008	20/05/2008	Annex II	On the basis of the data submitted since the Marketing Authorisation, the risk/benefit balance in the reduction of the number of adenomatous intestinal polyps in familial polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance, remains positive. The CHMP agreed to change the specific obligation set

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					out in Annex II.C to the Commission Decision and agreed that the Marketing Authorisation should remain under exceptional circumstances. The CHMP issued an Opinion on the annual re-assessment of the risk/benefit profile of Onsenal on 19 March 2008.
T/0014	Transfer of Marketing Authorisation Holder	06/12/2007	25/01/2008	SPC, Labelling, PL	
IB/0015	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	10/01/2008	n/a		
IB/0017	10_Minor change in the manufacturing process of the active substance	14/11/2007	n/a		
IA/0016	09_Deletion of manufacturing site	05/11/2007	n/a		
IA/0019	22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	31/10/2007	n/a		
IA/0018	22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new	31/10/2007	n/a		

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	manufacturer				
S/0012	Annual reassessment 3rd Annual-Reasessment	24/05/2007	25/07/2007	SPC, Labelling, PL	
IB/0010	10_Minor change in the manufacturing process of the active substance	12/07/2006	n/a		
IA/0011	08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	29/06/2006	n/a	Annex II, Labelling, PL	
IA/0008	09_Deletion of manufacturing site	02/06/2006	n/a		
IA/0007	05_Change in the name and/or address of a manufacturer of the finished product	02/06/2006	n/a		
A18/0005	Article 18 Review Further to a request from the European Commission to review the cardiovascular safety and the serious skin reactions of medicinal products containing celecoxib, etoricoxib, lumiracoxib, parecoxib or valdecoxib.	23/06/2005	05/10/2005	SPC, PL	Please refer to the scientific discussion: Onsenal-H-466-Art18-05

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S/0004	Annual reassessment First annual reassessment of Onsenal, as the approval was granted under exceptional circumstances.	16/03/2005	02/06/2005	SPC, Labelling, PL	Onsenal has been shown to be effective in reducing the size and number of colonic and duodenal polyps that lead to the development of colorectal cancer in patients with Familial Adenomatous Polyposis (FAP). Onsenal is the only medicinal product approved in the EU for FAP, as adjunct therapy in the current standard of care, which is surgery. Onsenal is not intended to alter standard surveillance or to replace the usual surgical management of the disease; nevertheless, it may prove useful in delaying surgery for specific reasons, or in the therapeutic management of patients who are inoperable. The concerns raised by the recent findings of possible increased cardiovascular (CV) risks from one long-term study in Sporadic Adenomatous Polyps (SAP) patients are considered. However, it is important to note that the FAP and SAP populations are very different: FAP patients are predominantly young, and, as such, are expected to have a low incidence of cardiovascular disease, while SAP is a disease which frequency increases with increasing age. In addition, in FAP there is a considerable risk of cancer and postoperative complications (that is not present in SAP), which somewhat balances the risk of cardiovascular serious adverse events.

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					Therefore, is seems justified to use a high-dose of Onsenal in the treatment in selected FAP patients, provided that there is a good routine surveillance and that physicians are aware of a possible increased risk for certain CV events. The CHMP, having reassessed the benefit-risk profile of Onsenal, and taking into account the Urgent Safety Restriction of 16 February 2005, as part of the second COX-II Inhibitors review, agreed to introduce the following amendments to the Product Information: · A contra-indication is introduced in patients with established ischaemic heart disease and/or cerebrovascular disease. · The warning on gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) has been strengthened. · A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking, as well as for patients with peripheral arterial disease. · A warning is introduced for prescribers to

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					exercise caution when prescribing NSAIDs, including celecoxib, in combination with ACE inhibitors or angiotensin II receptor antagonists. · Information on long-term studies for celecoxib in SAP and Alzheimer's disesase has been included. On the basis of the data submitted since the Marketing Authorisation, the risk/benefit in the reduction of the number of adenomatous intestinal polyps in familial polyposis (FAP), as and adjunct to surgery and further endoscopic surveillance, remains positive. The CHMP agreed that the Marketing Authorisation should remain under exceptional circumstances.
IB/0003	42_a_01_Change in shelf-life of finished product - as packaged for sale	10/11/2004	n/a	SPC	
IA/0002	01_Change in the name and/or address of the marketing authorisation holder	28/06/2004	n/a	SPC, Labelling, PL	