Enviage

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/0039	Update of the Detailed Description of the Pharmacovigilance system (DDPS). Changes to QPPV, Update of DDPS (Pharmacovigilance)	18/02/2010	23/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 6.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
II/0034	Update of Summary of Product Characteristics Update of SPC section 5.1 to delete the existing sentence relating to elevated plasma renin activity and cardiovascular outcomes.	19/03/2009	22/04/2009	SPC	The following sentence has been deleted from SPC section 5.1 based on the fact that currently no data are available to directly link the reduction in renin activity induced by aliskiren with effects on cardiovascular outcomes: “Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients.” as currently there is no evidence available proving that changes in renin activity induced by antihypertensive drugs might have an important role in cardiovascular disease.
II/0033	Update of Summary of Product Characteristics and Package Leaflet Update of SPC section 4.4 to include a warning of events of renal dysfunction in at-risk patients and to amend the existing text for renal artery stenosis following the CHMP assessment of PSURs. SPC section 4.8 has been updated relating to events of renal dysfunction and acute renal failure during post-marketing experience. The package leafet has been amended accordingly.	19/02/2009	03/04/2009	SPC, PL	For aliskiren, cases of renal dysfunction with relevant occurrence were reported in the postmarketing use (PSUR 1 and PSUR 2). Following evaluation of the available postmarketing data, the CHMP concluded to add a warning to SPC section 4.4 that caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolemia (eg. due to blood loss, severe or prolonged diarrhea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience.. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued. Furthermore, SPC section 4.8 was also amended.
II/0032	Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	03/04/2009	SPC, PL	The MAH was requested to add a statement regarding the potential for interaction between NSAID's and agents acting on the Renin

[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)

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	Update of SPC section 4.5 to include a statement regarding the potential interaction with non-steroidal anti-inflammatory agents (NSAIDs). The package leaflet has been amended accordingly.				Angiotensin System to SPC section 4.5. As with other agents acting on the renin -angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients. The package leaflet has been amended accordingly.
II/0031	Update of Summary of Product Characteristics and Package Leaflet Update of SPC sections 4.3 and 4.4 to include a contraindication on the use in patients with prior history of angioedema and a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system respectively, following the CHMP assessment of PSURs. Furthermore, SPC section 4.8 has been revised regarding angioedema cases and the Package Leaflet has been updated in accordance with the SPC changes.	19/02/2009	03/04/2009	SPC, PL	For aliskiren, cases of angioedema with relevant occurrence were reported in the postmarketing use. Following the assessment of the available data, the CHMP concluded that a contraindication for patients with a history of angioedema with aliskiren is needed. In addition, a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system has been added to SPC section 4.4 recommending that patients without a previous history who suffer angioedema with aliskiren should discontinue treatment and contact their doctor. Furthermore,the term "angioedema" has been added as a rare adverse drug reaction to SPC section 4.8.
II/0029	Update of or change(s) to the pharmaceutical documentation	23/10/2008	04/11/2008		
II/0026	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of SPC section 4.3 "Contraindications" and section 4.5 "Interactions" following new information from a cyclosporine drug-drug interaction study (SPP100A2106), which was subject to a Follow-Up Measure. Further revisions were introduced to section SPC sections 4.4 "Warnings and Precautions for use" and 4.5.	24/07/2008	28/08/2008	SPC, Labelling, PL	The results of the cyclosporine interaction study in 14 subjects showed that concomitant cyclosporine administration increased AUC 4.5 to 5.5 fold with a lower dose of aliskiren (75 mg) than the authorised strengths (150 and 300mg). Also cyclosporine markedly increased aliskiren t1/2. Hence, there is concern that the increase in AUC would be substantially higher with the approved aliskiren dosage, even exceeding the highest dose tested in humans. An additional concern is that aliskiren might distribute to tissues from which the medicinal product is normally absent in presence of a P-gp inhibitor, or preset at low levels because of the activity of P-gp. Non clinical and clinical data converge to show that P-gp is a major determinant of aliskiren bioavailability. In addition, literature data show that P-gp mediates

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	The package leaflet has been amended accordingly. In addition, minor corrections have been included in the relevant sections of SPC, labelling and package leaflet with regard to the active substance (aliskiren hemifumarate) and also for PL section 5.				tissue uptake of a variety of P-gp substrates and that P-gp inhibitors can markedly increase the tissue-to-plasma concentration ratios. Given the very limited safety data at increased exposure, and the risk for very large increase in tissue exposure, the CHMP concluded that the co-administration of cyclosporine and aliskiren poses serious safety concerns. Therefore, a contraindication for the concomitant administration with cyclosporine, a highly potent P-gp inhibitor, as well as with other potent P g inhibitors (verapamil, quinidine) is considered essential. Moreover, due to the risk for higher increase in tissue exposure than in plasma, caution should be advised during co administration with moderate P-gp inhibitors (ketoconazol, itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).
II/0030	Update of or change(s) to the pharmaceutical documentation	24/07/2008	29/07/2008		
II/0028	Update of Summary of Product Characteristics Update of SPC section 5.1 "Pharmacodynamic Properties" with efficacy data from a clinical study (study SPP100C2201) in patients with nephropathy.	30/05/2008	09/07/2008	SPC	Study SPP100C2201, a 6 monthly randomised, double-blind, placebo-controlled study investigated the effects of aliskiren (150mg / 300mg) on proteinuria in 599 patients with hypertension and Type II 2 diabetes mellitus in whom blood pressure had been previously controlled by means of an angiotensin receptor blocker (losartan) in combination with the optional use of other antihypertensive drugs (hydrochlorothiazide and/or amlodipine). The addition of 300mg aliskiren achieved an average reduction in the urinary albumin to creatinine (UACR) ratio of 12 mg/mmol (from 58 to 46 mg/mmol) compared to placebo. Aliskiren did not induce any significant effect on blood pressure or affect estimated GFR under these conditions. The clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Furthermore, aliskiren was associated with an increased frequency (4.2% vs. 1.9% for placebo) in serum potassium concentration (? 6 mmol/l).
II/0027	Update of Summary of Product Characteristics Update of the SPC section 4.4 and 5.1 following new information from a study (SPP100A2313) in patients with heart	30/05/2008	09/07/2008	SPC	Study SPP100A2313, a 12-week double-blind, randomised, placebo-controlled, 2-arm study of aliskiren 150 mg od added to standard therapy in patients with stable heart failure evaluated the overall safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in hypertensive patients with stable heart failure. The study included 302 patients with mild to moderate heart failure.

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	failure.				Addition of 150 mg aliskiren showed a reduction of BNP levels by 25 %, although the clinical significance of this reduction is unknown. No statistically significant differences in signs and symptoms of heart failure were found and overall grading of patients according to NYHA classification remained unchanged.

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IB/0038	33_Minor change in the manufacture of the finished product		29/04/2009
IB/0036	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release		29/04/2009
IA/0037	32_a_Change in batch size of the finished product - up to 10-fold		11/02/2009
IA/0035	07_a_Replacement/add. of manufacturing site: Secondary packaging site 07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms		11/02/2009
IB/0012	10_Minor change in the manufacturing process of the active substance 12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter		31/01/2008
IA/0020	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0019	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0018	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0017	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0016	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0015	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0014	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0013	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IB/0002	12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter		14/11/2007
IB/0001	12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter		14/11/2007

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