Agenerase

Procedural steps taken and scientific information after the authorisation
Changes made after 01/09/2004

For procedures finalised before 01/09/2004, please refer to module 8A

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0044	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.5 of the SPC to add paroxetine interaction information based on the drug-drug interaction study COL100880. Section 2 of the PL is updated accordingly.	19/11/2009	21/12/2009	SPC, PL	Results from study COL100880 showed that Cmax and AUC(0- τ) of paroxetine were decreased by 51% and 55% respectively when paroxetine 20 mg once daily was co-administered with fosamprenavir/ritonavir 700/100mg twice daily for 10 days in a group of healthy volunteers. The mechanism of this interaction remains unknown. Based on historical comparison, amprenavir and ritonavir pharmacokinetic parameters were not altered by paroxetine, suggesting no impact of paroxetine on amprenavir and ritonavir exposure. Therefore, if paroxetine is co-administered with amprenavir and ritonavir, the recommended approach is a dose titration of paroxetine based on a clinical assessment of antidepressant response. In addition, patients on stable dose of paroxetine who start treatment with amprenavir and ritonavir should be monitored for antidepressant response.
II/0042	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.4 and section 4.8 of the SPC to add a statement on monitoring and management of hyperglycemia and lipid (cholesterol/triglyceride) elevations based on data from the French Hospital HIV cohort and to change frequency category of the adverse drug reaction "hypercholesterolaemia" based on postmarketing data. Section 4 of the PL was	22/10/2009	20/11/2009	SPC, PL	Postmarketing data have shown that treatment with fosamprenavir (FPV) (the pro-drug of amprenavir) resulted in increases in the concentration of triglycerides and cholesterol. Physicians should therefore be recommended to perform triglyceride and cholesterol testing prior to initiating therapy with amprenavir and at periodic intervals during therapy. The precautionary statement regarding the monitoring of hyperglycaemia was brought in line with this wording. Blood glucose testing should be performed prior to initiating therapy with amprenavir and at periodic intervals during therapy. Based on the results of two 2 postmarketing studies (ESS100732 and APV109141) the frequency category of the adverse drug reaction "hypercholesterolemia" was

[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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	updated accordingly.				increased from "uncommon" to "very common" for FPV. For consistency this frequency was applied to amprenavir. The two large postmarketing studies have demonstrated that Grade 3-4 cholesterol elevations occur at higher incidences than initially observed.
II/0040	Update of Summary of Product Characteristics Update of section 4.3 and section 4.5 of the SPC to implement the class labelling text agreed by the CHMP in May 2008 on the combination of rifampicin with amprenavir given with concomitant low-dose ritonavir.	25/09/2008	28/10/2008	SPC	In 2005 an interaction study on saquinavir boosted with ritonavir together with rifampicin in healthy volunteers had to be prematurely discontinued due to an increased risk of hepatotoxicity associated with this co-administration. The mechanism for this interaction is not fully elucidated. It has been hypothesised that the predominant effect between the inducer effect of rifampicin and the inhibitor effect of the boosted protease inhibitors might depend on the boosted protease inhibitor involved. Lacking the results of specific interaction studies, the CHMP concluded as a conservative measure to reinforce the contraindication with rifampicin in section 4.4 and improve the guidance provided to physicians regarding the interaction of boosted protease inhibitors with rifampicin in section 4.5.
II/0039	Update of Summary of Product Characteristics Update of section 5.1 of the SPC with in-vivo resistance data based on relevant clinical trials with the ritonavir boosted fosamprenavir regimen.	24/04/2008	18/06/2008	SPC	Based on in-vivo amprenavir/fosamprenavir (a pro-drug of amprenavir) resistance studies in antiretroviral therapy (ART)-naïve, protease inhibitors (PI)-naïve, PI experienced and ART experienced patients, the product information was updated. No differences were observed between the resistance mutations selected by boosted and unboosted fosamprenavir and the analysis of the virological failure samples defined four main resistance pathways in ART-naïve or PI-naïve patients. Similar resistance patterns were observed in the paediatric patients compared with the adults. It is noted that amprenavir is not approved for use in ART-naïve or PI-naïve patients. The wording on PI experienced patients was also updated; certain mutations were deleted as they were not present or not treatment emergent (i.e., were already present initially before treatment).

II/0036	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the SPC further to a review of angioedema cases carried out by the Marketing Authorisation Holder (MAH) to include the adverse reaction angioedema. Consequently, the PL is updated.	13/12/2007	28/01/2008	SPC, PL	Amprenavir (APV) contains a sulphonamide moiety. Published literature acknowledges that sulphonamides have been associated with allergic reactions. Angioedema is often a feature of allergic reactions. As of 20 April 2007, 58 reports (3.6 % of all APV reports) were retrieved from the MAH's worldwide safety database. Fifty-four reports were excluded from review. The remaining four reports were reviewed and assessed. They did not provide strong evidence of a causal association - despite three cases showing a compatible time to onset with APV (30 minutes, same day, 4 days) - since important information on concurrent antiretrovirals was missing or an infectious cause could not be ruled out. However, based on evidence from clinical trials, angioedema can be associated with APV with the frequency category "uncommon".
II/0035	Update of Summary of Product Characteristics Update of the resistance data in section 5.1 of the SPC based on a cumulative summary of all emergent mutations observed during clinical trails with unboosted and boosted fosamprenavir in previously PI-naive as well as experienced patients.	18/10/2007	30/11/2007	SPC	Further to the annual review carried out by the Marketing Authorisation Holder on resistance and cross-resistance the clinical information on Telzir SPC has been updated with emergent mutations observed during clinical trails in adults and in paediatric patients with unboosted and boosted fosamprenavir in previously PI-naive as well as experienced patients.
II/0033	Update of Summary of Product Characteristics, Annex II and Package Leaflet Update of section 5.1 of the SPC to remove information related to protease inhibitors (PI)-naïve patients and to improve the current information on pre-treated children and on PI-experienced adults. Consequently, section 4.1 of the SPC for Agenerase oral solution was amended. Annex IIB was updated in line with the current submission cycle for Agenerase PSURs (3-yearly basis).	19/07/2007	30/08/2007	SPC, Annex II, PL	The clinical information on Agenerase SPC has been reviewed to better reflect the current use of amprenavir. Therefore, information on the use of Agenerase in protease inhibitor (PI)-naïve patients has been removed from the SPC as Agenerase is indicated in PI-experienced patients only. Furthermore, currently amprenavir (as Agenerase) is no longer recommended in clinical guidelines as part of HAART, so there was no clinical relevance to have information on PI-naïve patients in the SPC. The information on pre-treated children and on PI-experienced patients presented in the SPC has been improved.

II/0034	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.3, 4.4 and 4.5 of SPC and section 2 of the PL as regards the interaction with oral and parenteral midazolam, following CHMP request in March 2007.	21/06/2007	25/07/2007	SPC, PL	Based on available data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally than when it is injected. Therefore, the coadministration of Agenerase with orally administered midazolam is contraindicated, whereas caution should be used when Agenerase is co-administrated with an injection of midazolam. If Agenerase is co-administered with injectable midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered. Sections 4.3, 4.4 and 4.5 of the SPC and section 2 of the PL are updated with this information.
II/0028	Update of Summary of Product Characteristics To update section 5.1 of the SPC to provide recommendations with regards to the mutation predictive of virological response to amprenavir/ritonavir and to review available in vitro resistance data and assess the possibility of cross-resistance to newly licensed protease inhibitors (PI) such as lopinavir, atazanavir and tipranavir. This follows the CHMP's requests dated 21 September 2005 and 16 March 2006, respectively, further to the assessment of the renewal dossier for amprenavir, follow-up measure 019 for fosamprenavir as well as current clinical guidance on resistance.	22/02/2007	28/02/2007	SPC	During studies in PI-naïve patients treated with unboosted amprenavir (phase II studies PRO2001 and PRO2002 and Phase III pivotal studies PRO3001 and PRO3006), PI-mutations were identified. Although no resistance data is available for boosted amprenavir in PI naïve patients, in study PRO30017 (PI-experienced patients) mutations emerged in patients with virological failure. No clinical data is available for PI- naïve patients treated with boosted amprenavir as oral solution. HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47V or I54M mutations. Each of these four genetic patterns associated with reduced susceptibility to amprenavir produces some cross-resistance to ritonavir but susceptibility to indinavir, nelfinavir and saquinavir is generally retained. There are currently insufficient data on cross-resistance between amprenavir and other protease inhibitors. Based on data from thirteen antiretroviral naïve patients failing a fosamprenavir containing regimen and on limited in vitro data (site directed mutagenesis) the resistance pathways associated with amprenavir produce limited cross-resistance to lopinavir (clinical data available from thirteen isolates) while susceptibility to atazanavir (from four isolates) and tipranavir (from two isolates) is generally retained. Conversely amprenavir retains activity against some isolates with resistance to other PIs and this retained activity would depend on the number and type of protease resistance mutations present in the isolates

II/0030	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006.	14/12/2006	24/01/2007	SPC, PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multiple factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0029	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.5 of the SPC with the results of an interaction study comparing ketoconazole 200mg once daily and fosamprenavir/ritonavir 700/100mg twice daily in healthy volunteers. Section 6 of the PL was updated with the local representatives in Bulgaria and Romania.	16/11/2006	08/01/2007	SPC, PL	A specific drug interaction study to further substantiate the recommendation of co-administration of fosamprenavir/ritonavir with ketoconazole was submitted as part of the follow-up commitments made at the time of the marketing authorisation for fosamprenavir (Telzir). Results of this study can be extrapolated to Agenerase, as fosamprenavir is a pro-drug that is completely converted to amprenavir during absorption. Results of the study showed that ketoconazole pharmacokinetic parameters (essentially area under the curve, AUC) are significantly increased when ketoconazole 200 mg once daily is co-administered with fosamprenavir 700 mg twice daily boosted with ritonavir 100 mg twice daily. These results confirm that fosamprenavir boosted leads to an increase of ketoconazole AUC, which is much higher (2.69 fold) than with amprenavir unboosted (0.44 fold). No significant impact of ketoconazole on amprenavir and ritonavir exposures was observed. Consequently, the updated recommended maximum daily dose of this co-administration is not more than 200 mg ketoconazole once daily when given together with an amprenavir/ritonavir 700/100 mg twice-daily regimen.
II/0026	Update of Summary of Product Characteristics Update of section 5.1 of the SPC to harmonise its sub-section on resistance with the SPC of fosamprenavir. Also, addition of a sub-section on the mutations and number of mutations associated with the reduced virological response	23/03/2006	02/05/2006	SPC	Based on the SPC of Telzir (fosamprenavir) the resistance sub-section of the Agenerase SPC was updated to include mutation M46I/L based on in vitro data. Furthermore, the implications of the mutation I50V on a possible cross-resistance to nelfinavir were discussed. However, based upon an analysis to examine the nelfinavir anticipated response in subjects with isolates containing I50V after Agenerase failure, the CHMP concluded that a response to a subsequent nelfinavir-containing

	to ritonavir boosted amprenavir regimens (600mg/100mg twice daily).				regimen can be expected, provided an adequate active RTI (Reverse Transcriptase Inhibitor) backbone is combined. However, a boosted PI (Protease Inhibitor) regimen may be a more appropriate choice for salvage therapy following first-line PI failure. Furthermore, the cross-resistance section was updated with the inclusion of mutations and number of mutations associated with reduced virological response to subsequent amprenavir/ritonavir (600mg/100mgtwice daily) containing regimens. This was substantiated by a bibliographical reference (Marcelin et al, 2003), supporting the proposed table of mutations associated with an increased risk of treatment failure of amprenavir/ritonavir containing regimens.
R/0024	Renewal of the marketing authorisation	13/10/2005	17/11/2005	SPC, Annex II, Labelling, PL	Based on the CHMP review of the available information, the CHMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit risk balance of Agenerase continues to be favourable. The MA of Agenerase was renewed on conditions that the MAH complies with the following conditions: " Provision of updated cumulative reviews of convulsions, hallucinations, hepatic events, pancreatitis, hypersensitivity reactions, haemolytic anaemia, neutropenia, pancytopenia, prolongation of QT interval, arrhythmias, myocardial infarction, and sudden death within 2 months. " The MAH commits to continue to closely monitor the following reactions: immune reactivation syndrome, Guillain-Barré syndrome, and thrombotic thrombocytopenic purpura In addition, as a consequence of the ADRs, which require monitoring, it was recommended that the MAH should continue to submit yearly PSURs and not progress to a 3-year reporting cycle at this time. Furthermore, no new safety issues have been raised either in the latest PSUR or as part of the cumulative experience, which warranted any change in the Product Information at this time.

II/0025	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.4 and 4.5 of the SPC with the class labelling text on "fluticasone " following the CHMP Assessment Report on the "Interaction with ritonavir boosted protease inhibitors and fluticasone" dated 26 May 2005. Point 2 of the PL is amended accordingly.	27/07/2005	24/08/2005	SPC, PL	The MAH implements the class labelling on the fluticasone propionate-ritonavir interaction. This interaction is supported by the results of one multiple-dose crossover design clinical study in healthy subjects, conducted by GSK in July- October 2002 (Study FNM 10004). This study aimed at evaluating the effects of several CYP3A4 inhibitors, including ritonavir, ketoconazole and erythromycin on systemic concentrations of fluticasone after nasal inhalation.
II/0023	Update of Summary of Product Characteristics and Package Leaflet To update section 4.4 and 4.8 of the SPC and section 2 of the PL, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004.	18/11/2004	17/12/2004	SPC, PL	In patients treated with any type of combination antiretroviral therapy (CART), an inflammatory response to indolent or residual opportunistic infections may occur, when the immune system responds to treatment. In most cases, the inflammatory reactions towards the opportunistic pathogens in question cannot be foreseen since the opportunistic infection has not yet been detected/diagnosed. If diagnosed prior to institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared in this context; CMV-retinitis, generalised mycobacterial infections and Pneumocystis carinii pneumonia. An additional reason for treating the OI and the HIV-infection sequentially, is the great risk of adverse events (toxicity or lack of effect) due to drug interactions. In conclusion, in most cases, the clinical consequences of the awakening immune system in patients starting ART cannot be prevented. Therefore, early recognition and diagnosis of these inflammatory reactions are important in the clinical handling of the patient. The description and the guidelines for treatment of the numerous clinical conditions potentially arising in association with the reactivation of the immune system in HIV-infected patients are given in the textbooks of infectious diseases. However, as the clinical conditions associated with the reactivation of the immune system may constitute a threat to the patient, a reminder of the phenomenon is deemed of value and has been included in the SPC and PL of all antiretroviral medicinal products.

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0041	01_Change in the name and/or address of the marketing authorisation holder	SPC, Labelling, PL	24/02/2009
IA/0038	05_Change in the name and/or address of a manufacturer of the finished product	Annex II, PL	15/11/2007
IA/0037	09_Deletion of manufacturing site	Annex II, PL	15/11/2007
IB/0032	17_a_Change in re-test period of the active substance		02/02/2007
IA/0031	07_a_Replacement/add. of manufacturing site: Secondary packaging site		21/11/2006
IA/0027	22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer		03/04/2006

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