# Aluvia

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 |
|---|---|---|---|---|---|
| IAIN/0120 | B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings | 17/11/2023 | | SmPC and PL | |

[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).

| | | | | | |
|---|---|---|---|---|---|
| WS/2488 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 31/08/2023 | | SmPC and PL | On 27 January 2022, the Applicant was requested by the EMA to expand the Norvir (ritonavir) SmPC for the Drug-Drug Interactions (DDIs) of ritonavir with direct oral anticoagulants (DOACs) dabigatran and edoxaban to align with recent updates to the Prezista (darunavir) label. This request resulted from the Norvir LEG 033-12, which is the commitment to "… update the product information annually with any relevant information on boosted protease inhibitors that may be approved in the future."<br>Although in contrast to the situation for darunavir, no direct DDI data are available for ritonavir (and the combination of lopinavir and ritonavir) with dabigatran etexilate; from a mechanistic point of view, it is considered highly likely by the Committee that a comparable DDI between ritonavir (or lopinavir/ritonavir) with the P-gp substrates dabigatran etexilate and edoxaban will occur, leading to increased bioavailability of these DOACs. The Committee considers the above sufficiently supported by literature data (Testa S et al, 2020, publishing cases displaying such increased exposures).<br>Ritonavir is also an active ingredient of Kaletra (lopinavir/ritonavir) and Aluvia (lopinavir/ritonavir).<br>In this light, based on the above, sections 4.5 of the SmPCs of Norvir, Kaletra and Aluvia are updated to add the treatment recommendations for dabigatran exilate and edoxaban. The Package Leaflets (PL) are updated accordingly.<br>For more information, please refer to the Summary of Product Characteristics. |
| IG/1615 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process | 30/05/2023 | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| | of the AS | | | | |
| IG/1574 | 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 | 15/12/2022 | n/a | | |
| IB/0116 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 28/07/2022 | | SmPC and PL | |
| PSUV/0115 | Periodic Safety Update | 10/06/2022 | n/a | | PRAC Recommendation - maintenance |
| WS/1845 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.4: Update of section 4.5 of the SmPCs in order to add information on drug-drug interactions with fostamatinib. The Package Leaflets are updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 16/07/2020 | 16/07/2020 | SmPC and PL | Co-administration of fostamatinib with strong CYP3A4 inhibitors (e.g. ritonavir) may increase fostamatinib metabolite R406 exposure, resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea.<br>For more information, including information on dose reduction recommendations if such events occur, please also refer to the Summary of Product Characteristics of Tavlesse (fostamatinib). |
| WS/1842 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.8 of the SmPC in order to update | 02/07/2020 | | SmPC, Annex II, Labelling and PL | The proposed variation is based on a safety review conducted by MAH prompted by the publication in July 2019 from Zhao describing a patient who experienced a kidney stone composed entirely of ritonavir. Based on this, the product information of Kaletra and Aluvia |

| | | | | | |
|---|---|---|---|---|---|
| | the safety information for nephrolithiasis as an adverse reaction following an update to the Kaletra and Aluvia (lopinavir/ritonavir) and Norvir (ritonavir) Company Core Data Sheets (CCDS 0220). The Package Leaflet is updated accordingly.<br><br>In addition, the MAH/SOH takes the opportunity to make additional changes in the PI in order to comply with the current QRD template and provide clarity to instructions contained in the Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | (lopinavir/ritonavir) and Norvir (ritonavir) has been reviewed to update the safety information by adding "nephrolithiasis" as an adverse reaction with an unknown frequency.<br><br>For more information, please refer to the Summary of Product Characteristics. |
| WS/1711 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>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 | 12/03/2020 | n/a | | |
| WS/1705 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change of section 4.8 of the SmPC to update the | 31/10/2019 | | SmPC and PL | Based on the results of a cumulative safety review from all MAH-sponsored clinical studies identified with LPV/RTV in a total of 2,612 patients, the frequency of 3 adverse reactions has been modified: jaundice changed from "unknown" to "uncommon", since there were 6 reported |

| | | | | | |
|---|---|---|---|---|---|
| | safety information of Kaletra and Aluvia following a cumulative safety review of the incidence rate of Stevens-Johnson syndrome, erythema multiforme and jaundice during clinical trials. This variation closes LEG 110. The Package Leaflet is updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | cases among 2,612 patients; erythema multiforme changed from "unknown" to "rare", since there was one event reported and Stevens-Johnson syndrome (SJS) changed from "unknown" to "rare" since there was one case reported. |
| WS/1677 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.5 of the SmPC on the potential interaction with apalutamide, a moderate to strong CYP3A4 inducer, as well as with encorafenib, following an evaluation of the potential drug-drug interaction (DDI) between LPV/RTV (Kaletra and Aluvia) with apalutamide (Erleada) and encorafenib (Braftovi) through bibliographic and post-marketing data search. The Package Leaflet is also updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 19/09/2019 | 19/09/2019 | SmPC and PL | A bibliographic and post-marketing data search showed that the concomitant use of lopinavir (LPV)/ritonavir (RTV) (Kaletra and Aluvia) or ritonavir (Norvir) with apalutamide and encorafenib is not recommended. This is due to the fact that LPV/RTV are both inhibitors of CYP3A and the co-administration with apalutamide and encorafenib, both anticancer agents which are primarily metabolised by CYP3A, may result in increased plasma concentrations and lead to increased toxicity and potential risk for serious adverse events.<br>Additionally, apalutamide, an inhibitor of androgen receptors indicated for the treatment of prostate cancer, is a strong inducer of CYP3A4. The co-administration of apalutamide with LPV is expected to decrease LPV exposure and potentially lead to virological failure and resistance emergence. Given the metabolic properties of LPV, RTV and apalutamide, and that these three compounds are metabolised through CYP3A, the net effect of LPV/RTV and apalutamide combination is unpredictable and hence, their co-administration is not recommended. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Similarly, encorafenib, a kinase inhibitor indicated for the treatment of metastatic melanoma, is both an inhibitor and inducer of CYP3A4 and may also affect CYP3A4 substrates such as LPV/RTV. Given that its impact on LPV/RTV exposure is also unknown, its coadministration is not recommended. |
| WS/1588 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.3 and 4.5 of the SmPC in order to include information on the contraindication with neratinib and interactions with abemaciclib, neratinib and glecaprevir/pibrentasvir. In addition, the Worksharing applicant (WSA) took the opportunity to update section 4.5 of the SmPC of Kaletra and Aluvia to add information on the interaction of lopinavir/ritonavir with sofosbuvir/velpatasvir/voxilaprevir, as well as to remove information on the interaction with boceprevir and telaprevir. Furthermore, the quantity of tenofovir disoproxil has been amended in sections 4.5 and 5.1 of the Kaletra and Aluvia SmPCs (as requested during procedure WS 1555) as 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil . The Package Leaflets are updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 29/05/2019 | 29/05/2019 | SmPC and PL | Lopinavir and ritonavir are inhibitors of the P450 isoform CYP3A in vitro. Co-administration with medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and may increase the potential for serious and/or life threatening reactions. Therefore, concomitant use of ritonavir and lopinavir/ritonavir with neratinib and abemaciclib, are contraindicated.<br>Furthermore, ritonavir and lopinavir are inhibitors of OATP1B1, P-glycoprotein and BCRP. Therefore, concomitant administration of ritonavir and lopinavir/ritonavir and glecaprevir/pibrentasvir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.<br>Moreover, serum concentrations of sofosbuvir, velpatasvir and voxilaprevir may be increased due to P-glycoprotein, BCRP and OATP1B1/3 inhibition by lopinavir/ritonavir. Therefore, it is not recommended to co administer lopinavir/ritonavir and sofosbuvir/velpatasvir/ voxilaprevir due to a potential risk associated with increase in voxilaprevir exposure.<br>Based on these potential drug-drug interactions, sections 4.3 and 4.5 of the SmPC of the product information for ritonavir and lopinavir/ritonavir fixed-dose combination |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | have been updated to provide further guidance for use in combination with these medical products. |
| PSUSA/1905/ 201809 | Periodic Safety Update EU Single assessment - lopinavir / ritonavir | 16/05/2019 | n/a | | PRAC Recommendation - maintenance |
| WS/1486 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 25/10/2018 | 25/10/2018 | SmPC | |
| WS/1411/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.5 of the SmPC in order to update the safety information on the interaction with ibrutinib based on the company core data sheets. The Package Leaflet is updated accordingly.<br>Update of section 4.5 of the SmPC in order to update the safety information of ritonavir, lopinavir/ritonavir on the interaction with levothyroxine based on the PRAC signal final assessment report EMA/101535/2018 leading to decreased levothyroxine efficacy and hypothyroidis.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to | 13/09/2018 | 13/09/2018 | SmPC and PL | Serum concentrations of ibrutinib co-administration may be increased due to CYP3A inhibition by lopinavir/ritonavir. Co-administration of ibrutinib and ritonavir containing products may increase ibrutinib exposure which may increase the risk of toxicity including risk of tumor lysis syndrome. Co administration of ibrutinib and ritonavir containing products should be avoided. If the benefit is considered to outweigh the risk and ritonavir containing products must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.<br>Post marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending lopinavir/ritonavir treatment. |

| | | | | | |
|---|---|---|---|---|---|
| | new quality, preclinical, clinical or pharmacovigilance data | | | | |
| T/0104 | Transfer of Marketing Authorisation | 04/04/2018 | | SmPC, Labelling and PL | |
| IG/0891 | 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 | 20/03/2018 | n/a | | |
| WS/1178 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.3 and 4.5 of the SmPC in order to add new contraindications and interaction information of lopinavir/ritonavir with venetoclax, with elbasvir/grazoprevir and with ombitasvir/paritaprevir/ritonavir with or without dasabuvir based on the company's core data sheet; the package Leaflet is updated accordingly. In addition, the MAH/SOH is taking the opportunity to update section 4.5 of the SmPC to reflect information already contained in section 4.3 for drug-drug interactions with astemizole, terfenadine, pimozide, ergot alkaloids and cisapride.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance | 20/07/2017 | 20/07/2017 | SmPC and PL | |

| | | | | | |
|---|---|---|---|---|---|
| | data | | | | |
| WS/1077/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.3 and 4.5 of the SmPC in order to add information regarding the interaction of lopinavir/ritonavir and ritonavir with lurasidone and ranolazine. In addition, sections 4.4 and 4.5 of the SmPC are updated to add information regarding the interaction with triamcinolone. The Package Leaflet is updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 21/04/2017 | 21/04/2017 | SmPC and PL | The concomitant use of lopinavir/ritonavir or ritonavir and ranolazine (antianginal) or lurasidone (antipsychotic/neuroleptic) is contraindicated. This is because due to CYP3A inhibition by lopinavir/ritonavir, concentrations of ranolazine or lurasidone are expected to increase and this increases the potential for serious and/or life-threatening reactions.<br>Concomitant use of lopinavir/ritonavir or ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4, such as budesonide and triamcinolone, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. |
| II/0100 | Update of sections 4.2 and 5.1 of the SmPC in order to update information following the analysis of the published 48-week study results "Kaletra ONCE daily randomised Trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1–infected children" (PENTA 18/KONCERT) in fulfilment of a Post Authorisation Measure (Additional PhV activity in the | 15/12/2016 | | SmPC | At week 48, the efficacy and safety with twice-daily dosing (n=87) in the paediatric population given lopinavir/ritonavir 100 mg/25 mg tablets was consistent with the efficacy and safety findings in previous adult and paediatric studies using lopinavir/ritonavir twice daily. The percentage of patients with confirmed viral rebound >50 copies/ml during 48 weeks of follow-up was higher in the paediatric patients receiving lopinavir/ritonavir tablets once daily (12%) than in patients receiving the twice-daily dosing (8%, p = 0.19), |

| | | | | | |
|---|---|---|---|---|---|
| | Risk Management Plan). In addition, the SOH takes the opportunity to remove the Missing Information safety concern of Limited Information of the Aluvia 100 mg/25 mg film-coated tablets in the paediatric population as part of the agreed RMP version 8.1.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | mainly due to lower adherence in the once-daily group. The efficacy data favouring the twice-daily regimen are reinforced by a differential in pharmacokinetic parameters significantly favouring the twice-daily regimen.<br>Based on the current data available, Aluvia should not be administered once daily in paediatric patients. |
| II/0099 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 15/09/2016 | | SmPC, Labelling and PL | |
| II/0098 | Update of sections 4.3 and 4.5 to add information regarding the interaction of lopinavir/ritonavir and dronedarone. In addition, Sections 4.3, 4.4 and 4.5 have been updated to include information regarding the contraindication with colchicine in patients with renal or hepatic impairment and in patients with normal renal or hepatic function if strong CYP3A4-inhibitor (such as ritonavir-boosted PI) is coadministered. The Labelling is updated accordingly. In addition the MAH took the opportunity to update sections 4.4 and 4.8 to change "immune reactivation syndrome" to "immune reconstitution inflammatory syndrome" to reflect current terminology.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 21/07/2016 | | SmPC and PL | |

| | | | | | |
|---|---|---|---|---|---|
| PSUSA/1905/201509 | Periodic Safety Update EU Single assessment - lopinavir / ritonavir | 13/05/2016 | n/a | | PRAC Recommendation - maintenance |
| IG/0660/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing | 23/02/2016 | 23/02/2016 | Annex II and PL | |
| II/0094 | Update of sections 4.4 and 4.5 of the SmPC in order to add information regarding the interaction between Lopinavir/ritonavir and delamanid. The Package Leaflet is updated accordingly. In addition, the Scientific opinion Holder (SOH) took the opportunity to bring the PI in line with the latest QRD template version 9.1.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 18/02/2016 | | SmPC, Annex II, Labelling and PL | Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended. |
| IB/0093 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 21/12/2015 | | SmPC and PL | |

| | | | | | |
|---|---|---|---|---|---|
| IAIN/0095 | A.1 - Administrative change - Change in the name and/or address of the MAH | 15/12/2015 | n/a | | |
| II/0092 | Update of sections 4.4 and 4.5 of the SmPC to add information on interaction of lopinavir/ritonavir and bedaquiline. The Package Leaflet has been updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 24/09/2015 | | SmPC and PL | |
| II/0089 | Update of SmPC sections 4.2, 5.1 and 5.2 with information regarding the pharmacokinetic profile, safety and efficacy of twice-daily (BID) versus once-daily (QD) dosing as part of combination antiretroviral therapy in paediatric patients, based on an analysis of the 24-week interim study report for study PENTA 18/KONCERT.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 26/02/2015 | | SmPC | The data submitted within this procedure confirmed that the current twice daily dosing of Aluvia provides adequate efficacy and safety in paediatric patients. |
| II/0088 | Update of SmPC section 4.5 to add information regarding the interaction between lopinavir/ritonavir and simeprevir. The Package Leaflet has been updated accordingly.<br>Further, the SOH proposes to update the Package Leaflet, upon request by the CHMP, in order to | 20/11/2014 | | SmPC and PL | In this variation the SmPC has been updated with information on the interaction between antiviral medicines: Aluvia (lopinavir/ritonavir) and Olysio (simeprevir). Further, the Package Leafle has been updated in order to provide more specific advice to patients if they forget to take a dose of Aluvia. |

| | | | | | |
|---|---|---|---|---|---|
| | provide more specific advice to patients if they forget to take a dose of Aluvia.<br>In addition, minor editorial changes have been introduced throughout the Product Information.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| IA/0091 | A.7 - Administrative change - Deletion of manufacturing sites | 06/10/2014 | n/a | | |
| IG/0476 | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location | 24/09/2014 | n/a | | |
| II/0083 | To add an alternative method of manufacture for the active substance<br><br>B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product | 26/06/2014 | n/a | | |
| IA/0087 | A.7 - Administrative change - Deletion of manufacturing sites | 15/05/2014 | n/a | | |
| II/0084 | Update of sections 4.2, and 5.2 to include dosing recommendation for HIV-1-infected women during | 25/04/2014 | | SmPC, Labelling and | Lopinavir/ritonavir has no dosing recommendations for HIV-infected women during pregnancy. LPV/r is listed in |

| | | | | | |
|---|---|---|---|---|---|
| | pregnancy and postpartum. In addition, section 4.6 was updated with results from the Antiretroviral Pregnancy Registry.<br>The Package leaflet is updated in accordance.<br>Minor corrections to align with QRD 9 were also made to Annex IIIA Labelling (heading 6) and Annex IIIB Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | PL | treatment guidelines as preferred protease inhibitor during pregnancy with the goal of treatment being full plasma HIV RNA suppression, defined as confirmed plasma HIV RNA < 50 copies/mL, by the third trimester of pregnancy and specifically by delivery. The MAH proposed the inclusion of dosing recommendations (the standard adult dose 400/100 mg BID) for HIV-1-infected women during pregnancy and postpartum based on clinical data and literature review.<br>Pharmacokinetic and clinical studies showed comparable efficacy of the standard regimen 400/100 mg BID, based on the suppression of plasma HIV-1 RNA in pregnant women and prevention of MTCT (mother to child transmission).<br>Overall, the standard LPV/r dose 400/100 mg BID in pregnant women provides adequate LPV exposure. However, caution should be warranted for subjects with HIV harbouring PI mutations as described in the literature. Since neither PK nor clinical studies are available to evaluate the risk of virologic failure or safety with once daily dosing of LPV/r during pregnancy, the once daily dosing to treat pregnant women is not recommended.<br>The safety of LPV/r 400/100 mg BID during pregnancy is supported by many available data from clinical studies, APR and post-marketing experience. The birth defects risk is unlikely in humans, but some studies observe an increase of prematurity in women receiving PIs (and notably LPV/r). However, this risk is not clearly identified and varies between studies.<br>In conclusion, the available data support the use of standard LPV/r dose 400/100 mg BID during pregnancy and post-partum. |

| | | | | | |
|---|---|---|---|---|---|
| IB/0086 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 11/04/2014 | | SmPC and PL | |
| IB/0082/G | This was an application for a group of variations.<br><br>B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS<br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate | 10/02/2014 | n/a | | |
| II/0079 | Update of sections 4.2 and 5.2 of the SmPC to add weight based (WB) dosing recommendations for paediatric patients to the Aluvia 100 mg/25 mg film coated tablets.<br>Further to CHMP request, section 4.5 of the SmPC was revised to include updated information on the concomitant use of non-nucleoside reverse transcriptase analogues and to remove information on nelfinavir. The update of section 4.5 applied to all Aluvia pharmaceutical forms/strengths.<br>In addition, spelling mistakes were corrected and headings in the PL to lower case were changed to comply with the QRD template version 9.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a | 19/12/2013 | | SmPC and Annex II | substudy from study PENTA 18 was performed to support the weight based dosing recommendations.<br>Pharmacokinetics assessments were obtained to test three doses regimen (2, 3 or 4 LPV/rtv 100/25 mg tablets BID) in the following body weight bands: ≥ 15 to ≤ 25 kg; > 25 to ≤ 35 kg; > 35 kg.<br>The pharmacokinetics parameters AUC0-12h, Cmax and Cmin of LPV/rtv were similar between these 3 weight bands. Moreover, AUC0-12h was equivalent to that of previous studies M05-730 (LPV/rtv tablets 400/100 mg BID in adults) and M98-940 (LPV/rtv oral solution at 300/75 mg/m2 in children), where doses were considered safe and effective in the paediatric population. The extrapolation of PK parameters obtained with lopinavir/ritonavir tablets to the oral solution showed a similar AUC0-12h when LPV/rtv oral solution is used at 10/2.5 mg/kg BID. |

| | | | | | |
|---|---|---|---|---|---|
| | 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 | | | | Overall, although these data are limited they support the inclusion of additional paediatric dosing recommendation based on body weight in the product information of the lopinavir/ritonavir tablet formation. |
| II/0080 | Update to sections 4.3, 4.4 and 4.5 of the Summary of Product Characteristics (SmPC) for Aluvia to add information regarding the interaction between Lopinavir/ritonavir and avanafil as well as the addition of quetapine as a contraindication as requested by the CHMP. Consequential changes are introduced in the Package Leaflet.<br>Change of the pharmaco-therapeutic group from "protease inhibitors" to "antivirals for treatment of HIV infections, combinations in section 5.1 as a consequence to the change in the ATC code.<br>Update of the information for the Romanian local representative and to align the Product Information with the QRD template version 9.0.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 21/11/2013 | | SmPC, Labelling and PL | This variation application proposed the update to sections 4.3, 4.4 and 4.5 of the Summary of Product Characteristics (SmPC) for Aluvia to add information regarding the interaction between lopinavir/ritonavir and avanafil (indicated for the treatment of erectile dysfunction in adult men) as well as the addition of quetapine (an antipsychotic) as a contraindication as requested by the CHMP.<br>Data on drug-drug interaction between avanafil and ritonavir were presented at American College of Clinical Pharmacology 2012 annual meeting. The study showed a 13-fold increase in avanafil AUCinf when co-administered with ritonavir 600 mg BID demonstrating the major involvement of CYP3A in its metabolism. A similar effect is expected with lopinavir/ritonavir. Based on the study results, the use of avanafil in combination with lopinavir/ritonavir was added as a contra-indication.<br>Drug-drug interaction with quetiapine resulting in deep come was identified as a signal and as a consequence the CHMP endorsed the PRAC recommendation to add this information in section 4.5 and include the contra-indication for concomitant use with quetiapine. |
| IG/0379 | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location | 15/11/2013 | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| IA/0078 | A.6 - Administrative change - Change in ATC Code/ATC Vet Code | 14/05/2013 | | SmPC | |
| IG/0263 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 28/01/2013 | n/a | | |
| II/0074 | Update of section 4.4 Special warnings and precautions for use as well section 4.8 Undesirable effects of the Summary of Product Characteristics (SmPC) for Aluvia to add information regarding autoimmune disorders to the information provided for Immune Reactivation Syndrome. Consequential changes were introduced to the Package Leaflet. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. Changes in the Annex II regarding Pharmacovigilance system, PSUR and RMP were introduced.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 17/01/2013 | | SmPC, Annex II and PL | Antiretroviral treatment leads to immune reconstitution, which might be responsible of Immune Reconstitution and Inflammatory Syndrome (IRIS) and patients might be at increased risk for autoimmune diseases. A literature review showed a relation between IRIS and autoimmune disease. Although a direct causal relation between IRIS and autoimmune disorders might be possible, there are many other risk factors to take into consideration that may contribute to the pathogenesis of these diseases. There is further evidence available supporting the occurrence of Graves' Disease following HAART therapy in HIV infected patients, because of nucleotide and amino acid homology between a unique region of the human thyrotropin receptor and the HIV-1 nef protein with demonstrated immune cross-reactivity between these two proteins. Although critical data comparing treated and untreated patients is currently not available, patients with severe immunodeficiency at commencing HAART therapy appear to be at increased risk. There are no data available showing an increased risk with a particular HAART regimen. The incidence of these autoimmune diseases is rare but it warrants the revision of relevant sections of the Product Information. |

| | | | | | |
|---|---|---|---|---|---|
| IG/0240/G | This was an application for a group of variations.<br><br>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS<br>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS<br>A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release<br>A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) | 14/12/2012 | 14/12/2012 | Annex II and PL | |
| IA/0075 | B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size | 23/11/2012 | n/a | | |
| II/0073/G | This was an application for a group of variations.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data<br>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with | 19/07/2012 | n/a | SmPC and PL | The medicinal product Aluvia is a co-formulation that contains lopinavir/ritonavir and it is acknowledged that ritonavir as an inducer of glucuronidation may increase the concentrations of drugs the metabolism of which is mainly dependent of this pathway. Pharmacokinetics as well as safety data of the following medicinal products maraviroc, boceprevir, telaprevir, rivaroxaban, lamotrigine, valproate and raltegravir were evaluated when these were co-administered with lopinavir/ritonavir. Consequently |

| | | | | | |
|---|---|---|---|---|---|
| | NO new additional data are submitted by the MAH | | | | information on these drug-dug interactions and clinical recommendations were introduced in the appropriate sections of the Aluvia Product Information. |
| IA/0072/G | This was an application for a group of variations.<br><br>B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition<br>B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place | 30/03/2012 | n/a | | |
| IB/0071 | B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size | 22/03/2012 | n/a | | |
| IA/0070 | B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 17/02/2012 | n/a | | |
| IAIN/0068 | 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 | 03/02/2012 | n/a | | |
| II/0063 | Update of sections 4.3 and 4.5 of the SmPC with the available drug interaction data about | 19/01/2012 | n/a | SmPC, Annex | Drug interaction data between lopinavir/ritonavir and alfuzosin, bosentan, colchicine, fusidic acid, salmeterol and |

| | | | | | |
|---|---|---|---|---|---|
| | lopinavir/ritonavir and bosentan, colchicine, tadalafil, alfuzosin fusidic acid and salmeterol. The PL was updated in accordance. In addition, the SOH took the opportunity to update version number of the Risk Management Plan in Annex II.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | II and PL | tadalafil were evaluated and as a consequence these data are reflected in section 4.5 of the SmPC. In addition, recommendations for the co-administration of alfuzosin, colchicine and fusidic acid were added to section 4.3 of the SmPC. |
| IB/0067 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 11/01/2012 | n/a | SmPC | |
| IA/0066 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 02/12/2011 | n/a | | |
| IG/0108/G | This was an application for a group of variations.<br><br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<br>C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database<br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of | 30/09/2011 | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| | pharmacovigilance obligations and described in the DD<br>C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | | | | |
| IB/0062 | To update the information on the interaction of lopinavirlritonavir and rifabutin provided in Section 4.5 Interaction with other medicinal products and other forms of interaction of Annex I (the Summary of Product Characteristics (SmPC)) to include the changes recommended by the CHMP.<br>The CHMP requested the SOH submit a variation to implement the following wording regarding the interaction with rifabutin:<br>"When given with Aluvia the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin.<br>Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of | 28/06/2011 | n/a | SmPC | |

| | | | | | |
|---|---|---|---|---|---|
| | rifamycin resistance and a treatment failure. No dose adjustment is needed for Aluvia. "<br><br>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH | | | | |
| II/0061 | Update of Summary of Product Characteristics<br>Update of section 4.6 of the SmPC to include information from the antiretroviral pregnancy registry concerning the risk of congenital birth defects and the use of lopinavir/ritonavir during pregnancy, following the assessment of PSUR 13. In addition, section 4.6 was updated to comply with the current SmPC guideline (GL), the QRD product information template and the GL of risk assessment of medicinal products on human reproduction and lactation: from data to labelling. The SOH took the opportunity to update section 4.1 of the SmPC in line with the HIV GL and to align the Aluvia Annexes, where appropriate, with the changes of the Kaletra Annexes adopted by the CHMP during the Renewal procedure.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 17/03/2011 | n/a | SmPC | The sample size in the Antiretroviral Pregnancy Registry for lopinavir/ritonavir is sufficient to detect a 2.4-fold increase in the overall risk for congenital birth defects in women exposed to lopinavir/ritonavir during pregnancy. Data from the APR from 2000 through 2007 showed an overall birth defect prevalence of 2.4% among women exposed to lopinavir/ritonavir at any time during pregnancy and a birth defect rate of 1.9% among those exposed during the critical first trimester.<br>The latest update with data cut off as of January 31, 2010 reported the rate of congenital birth defects in infants exposed to lopinavir/ritonavir during the first trimester to be similar to the rate reported previously. As of January 31, 2010, 1,986 infants were exposed to lopinavir/ritonavir during first trimester, and second and/or third trimesters with a rate of congenital birth defects in first trimester (n = 590) exposures of 1.7% (95% CI: 0.8 to 3.1).<br>Based on the above findings, the CHMP agrees to update Section 4.6 of the SmPC to reflect APR findings on congenital birth defects associated to lopinavir/ritonavir exposure during first trimester in pregnancy. The CHMP believes that this additional information will provide more |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | information to help prescribers weigh the benefits and risks for use of lopinavir/ritonavir during pregnancy. The CHMP also acknowledged that the APR is an ongoing study and as additional data becomes available, the language might need future revision, if appropriate. |
| II/0060 | Update of Summary of Product Characteristics and Annex IIB.<br>Update of Section 4.4 of the SPC to provide information about the risk of hepatotoxicity in HIV-uninfected patients and remind the prescriber that this risk also exists in HIV mono infected patients.<br>Annex IIB is updated to reflect the new Risk Management Plan version number 4, and to delete the reference made to the version number of the Detailed Description of the Pharmacovigilance System.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 17/02/2011 | n/a | SmPC and Annex II | A data review on hepatotoxicity with LPV/r was performed and due to the systematic associated treatment during post exposure prophylaxis, it was difficult to assess a causal relationship between LPV/r and hepatotoxicity. However, in all these cases the role of LPV/r could not be ruled out. Consequently, the SOH proposed to add a warning in the product information in section 4.4 of the SmPC and provide information about the risk of hepatotoxicity in individuals treated for post-exposure prophylaxis as well as to remind prescribers about this risk in HIV mono infected patients as well. The CHMP therefore agreed that close monitoring is needed in patients treated with LPV/r for a PEP indication. The CHMP also agreed that the results of the data review do not affect the benefit/risk balance of Aluvia. The routine pharmacovigilance risk minimisation activities for monitoring the risk of hepatotoxicity in mono infected and individuals treated for PEP proposed by the SOH were endorsed by the CHMP. |
| IG/0022/G | This was an application for a group of variations.<br><br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) | 22/09/2010 | n/a | Annex II | |

| | | | | | |
|---|---|---|---|---|---|
| | to the DDPS that does not impact on the operation of the pharmacovigilance system | | | | |
| IB/0059 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 21/09/2010 | n/a | | |
| IB/0058 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 21/09/2010 | n/a | | |
| IB/0057 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 21/09/2010 | n/a | | |
| IA/0056 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 05/08/2010 | n/a | | |
| IG/0014/G | This was an application for a group of variations.<br><br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD | 23/07/2010 | n/a | Annex II | |

| | | | | | |
|---|---|---|---|---|---|
| IA/0054 | B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method | 23/07/2010 | n/a | | |
| IA/0053 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 23/07/2010 | n/a | | |
| II/0049 | Update of section 4.8 of the SmPC based on a full analysis of the frequency and the causality of the Adverse Drug Reactions in lopinavir/ritonavir clinical trials database in fulfilment of a follow-up measure. In addition the section is revised in accordance with the Guideline on SmPC rev 2. Consequently the PL is updated.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 22/07/2010 | n/a | SmPC and PL | The SOH proposed to update the section 4.8 of the SmPC following the Guideline on the SmPC. Furthermore it has been proposed to add and delete certain Adverse Drugs Reactions following an algorithm provided by the SOH which analyse the frequency and the causality of the Adverse events and the Adverse Drug Reactions. Moreover, hepatitis, Jaundice, Stevens-Jonhson syndrome and erythema multiform have been added to the tabulated summary with a not known frequency. The PL has been updated accordingly. |
| II/0048/G | This was an application for a group of variations.<br><br>This was an application for a group of variations. In section 5.1 of the SmPC, the sub section on resistance is updated in fulfilment of FUM 020. In fulfilment of FUM 018, further changes to section 5.1 are made in line with the Annex B of the Guideline on Clinical Development of Medicinal Products for | 22/07/2010 | n/a | SmPC | In section 5.1 of the SmPC, the sub section on resistance is updated in fulfilment of FUM 020. The sub-section "Analysis of resistance in ARV-naïve patients" was simplified and the description of study M97-720 and study M98-863 was transferred to the sub section "Patients without prior antiretroviral therapy".<br>In fulfilment of FUM 018, changes to section 5.1 are made in line with the Annex B of the Guideline on Clinical |

| | | | | | |
|---|---|---|---|---|---|
| | Treatment of HIV Infection. In addition, in fulfilment of FUM 026, references to the lack of clinical experience with lopinavir/ritonavir are being deleted in section 4.1.<br><br>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<br>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH | | | | Development of Medicinal Products for Treatment of HIV Infection.<br>Finally, in fulfilment of FUM 026, references to the lack of clinical experience with lopinavir/ritonavir are being deleted in section 4.1 |
| IA/0055 | A.1 - Administrative change - Change in the name and/or address of the MAH | 20/07/2010 | n/a | | |
| IB/0050 | To revise the wording for storage conditions from "This medicinal product does not require any special storage conditions" to "Store Below 30°C".<br><br>B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product | 13/07/2010 | n/a | SmPC, Labelling and PL | |
| II/0047 | Update of section 4.5 of the SmPC in line with the latest version of the Company Core Data Sheet (CCDS) based on a pharmacokinetic analysis of | 24/06/2010 | n/a | SmPC and PL | Following some drug interaction studies between lopinavir/ritonavir and two signal transduction inhibitors, dasatinib and nilotinb, which are used in the treatment of |

| | | | | | |
|---|---|---|---|---|---|
| | lopinavir/ritonavir and fentanyl, nilotinib and dasatinib. Consequently, the PL was updated. In addition, the SOH took this opportunity to update the name of Pneumocystis jiroveci in the SmPC.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | chronic myelogenous leukaemia (CML), and fentanyl which is used in pain management the Interaction Table in the section 4.5 of the SmPC has been updated.<br>These drugs are metabolised by CYP3A4 enzymes which are inhibited by Aluvia, therefore there is a potential interaction with increased risk in frequency and intensity of adverse events.<br>The Package Leaflet has been updated accordingly. |
| II/0043 | The SOH applied for an update of sections 4.2, 4.5, 4.8 and 5.1 of the SPCs based on the Phase III study M06-80 in support of a once-daily dosing regimen in antiretroviral experienced patients. The PL was updated in accordance.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 18/02/2010 | n/a | SmPC and PL | A phase 3, randomised, open-label multicentre study of lopinavir/ritonavir tablets 800/200 mg once-daily versus 400/100 mg twice-daily when co-administered with Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) in antiretroviral-experienced, HIV-1 infected patients showed that the once-daily regimen led to comparable results in terms of antiviral activity to the twice-daily regimen in moderately Protease Inhibitor (PI)-experienced patients. Therefore, the CHMP considered that the once-daily regimen is acceptable for patients with viral strains harbouring limited PI mutations and having low viral load. However, the once-daily regimen is to be avoided in patients with a high viral load and/or harbouring viral strains with 3 or more PI mutations; also, patients with certain co-medications (i.e. efavirenz, nevirapine, amprenavir, nelfinavir, phenytoin, carbamazepine and phenobarbital) must not use lopinavir/ritonavir once-daily. The CHMP further considered that the safety profile of the once-daily regimen was consistent with the one observed in previous studies conducted with lopinavir/ritonavir and that no new safety signal had been identified. |

| | | | | | |
|---|---|---|---|---|---|
| IB/0044 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 26/01/2010 | n/a | | |
| IA/0046 | IA_13_a_Change in test proc. for active substance - minor change | 11/01/2010 | n/a | | |
| IA/0045 | IA_28_Change in any part of primary packaging material not in contact with finished product | 11/12/2009 | n/a | | |
| II/0042 | Update of Detailed Description of the Pharmacovigilance System.<br><br>Update of DDPS (Pharmacovigilance) | 19/11/2009 | 19/11/2009 | Annex II | The Scientific Opinion Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated using standard text including the number of the version agreed for the DDPS (version 3). |
| II/0040 | Update of section 4.5 of the SmPC based on literature data regarding the interaction of lopinavir/ritonavir and tipranavir. The PL was updated in accordance.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 22/10/2009 | 22/10/2009 | SmPC and PL | In a clinical study of dual boosted protease inhibitor combination therapy in multiple treatment experienced HIV 1 infected adults, tipranavir (500 mg twice daily) with ritonavir (100 mg twice daily), co administered with lopinavir/ritonavir (400/100 mg twice daily), resulted in a 70% reduction in lopinavir Cmin. Due to this reduction in lopinavir exposure, the CHMP concluded that this co-administration should be avoided. |
| II/0036 | Update of sections 4.2 and 4.4 of the SmPC in order to update information on the use of lopinavir/ritonavir in patients with renal impairment. The SOH also took the opportunity to reformat section 4.5 of the SmPC in line with the Annex A to the guideline on Clinical Development of Medicinal Products for Treatment of HIV Infection as requested by the CHMP. As a consequence, sections 4.3 and | 22/10/2009 | 22/10/2009 | SmPC and PL | The CHMP acknowledged that renal impairment may affect the pharmacokinetics of a medicinal product not only by modifying its clearance but also its distribution or its absorption. Therefore, caution is generally warranted for any medicinal product used in patients with renal impairment. However, this general caution applies to all medicinal products when treating patients with sever renal impairment. In view of the pharmacokinetics of |

| | | | | | |
|---|---|---|---|---|---|
| | 4.4 of the SmPC and the PL were updated as well. In addition, a minor mistake in section 5.1 relating to resistance data was corrected.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | lopinavir/ritonavir (negligible renal clearance), the CHMP concluded that there is no reason to include a specific warning regarding the use of Aluvia in severe renally impaired patients. In addition, based on the review of updated Aluvia interaction data, information on statins and sildenafil was updated. |
| II/0029 | Update of sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SPC based on data from ongoing pharmacokinetic study M05-730 to add the possibility of a once-daily dosing regimen for antiretroviral treatment naïve patients. In addition, the SOH took this opportunity to update section 4.8 of the SPC to exchange the currently used COSTART terms to MedDRA terminology. Consequently, the PL was updated.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 23/07/2009 | 23/07/2009 | SmPC and PL | Study M05-730 was a randomised, open-label, multicentre trial comparing treatment with Aluvia 800/200 mg once daily plus tenofovir DF and emtricitabine versus Aluvia 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. The results of the study showed that the once daily regimen of Aluvia tablets was statistically non-inferior to the twice daily regimen, therefore, the CHMP agreed to add this option to the Aluvia SPC for the tablet formulations. However, there were some indicators that in regards to long-term viral suppression the twice-daily regimen might be more optimal. Also, the once daily regimen showed a higher rate of diarrhoea. Cautionary statements highlighting these limitations were therefore added to the new posology option |
| IA/0039 | IA_09_Deletion of manufacturing site | 30/03/2009 | n/a | | |
| IB/0037 | IB_42_a_01_Change in shelf-life of finished product - as packaged for sale | 01/12/2008 | n/a | SmPC | |
| IA/0038 | IA_37_a_Change in the specification of the finished product - tightening of specification limits | 24/11/2008 | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| IB/0034 | IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance | 21/11/2008 | n/a | | |
| IA/0035 | IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec. | 06/11/2008 | n/a | | |
| II/0031 | Update of Detailed Description of the Pharmacovigilance System<br><br>Update of DDPS (Pharmacovigilance) | 23/10/2008 | 23/10/2008 | Annex II | The Scientific Opinion Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated using standard text including the number of the version agreed for the DDPS (version 2). |
| IB/0033 | IB_10_Minor change in the manufacturing process of the active substance | 10/10/2008 | n/a | | |
| IB/0032 | IB_10_Minor change in the manufacturing process of the active substance<br>IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) | 07/10/2008 | n/a | | |
| II/0025 | Update of section 5.1 of the SPC, subsection "Resistance" to reflect data from international HIV drug resistance databases.<br><br>Update of Summary of Product Characteristics | 25/09/2008 | 25/09/2008 | SmPC | Based on data available from international HIV drug resistance databases, the current information on the lopinavir/ritonavir mutation score was updated by adding the mutations I47A and L76V in the information for protease inhibitor experienced patients receiving Aluvia therapy. In addition, a sentence was added to the resistance section of the SPC to highlight the necessity to always consult current interpretation systems for analysing resistance test results. |
| II/0026 | Update of sections 4.2 and 4.5 of the SPC with recommendations regarding co-administration of | 26/06/2008 | 26/06/2008 | SmPC | On the basis of pharmacokinetic data extracted from 4 clinical studies (3 in healthy volunteers and 1 in HIV- |

| | | | | | |
|---|---|---|---|---|---|
| | fosamprenavir and lopinavir/ritonavir (concomitant administration of these medicinal products is not recommended) following assessment of a clinical follow-up measure.<br><br>Update of Summary of Product Characteristics | | | | infected patients) investigating the recommended dosage regimens for fosamprenavir and lopinavir/ritonavir and other regimens with an increase of fosamprenavir dosage, of lopinavir dosage or of ritonavir dosage, the Product Information of Aluvia was amended. Dosage recommendations and data on co-administration of lopinavir/ritonavir with fosamprenavir have been deleted from sections 4.2 and 4.5 of the SPC and replaced by a non-recommendation of concomitant use of lopinavir/ritonavir with fosamprenavir. |
| II/0024 | Update of section 4.5 of the SPC based on the 10th PSUR to include the potential interaction between lopinavir/ritonavir and bupropion. Consequently, section 2 of the PL was updated.<br>In addition, the SOH took this opportunity to revise the SPC to incorporate QRD comments made during the assessment of a recent line extension application, to reflect the results of the user testing for the PL, as well as to update the contact details of the Italian local representative in the PL.<br><br>Finally, a change is proposed to the section 16 (Information in Braille) of the Labelling to correct the strength on the carton for Aluvia 100mg/25mg tablets.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 26/06/2008 | 26/06/2008 | SmPC, Labelling and PL | In this study, twelve healthy volunteers received a single 100 mg dose of sustained-release bupropion before and after 2 weeks of treatment with lopinavir/ritonavir 400 mg/100 mg twice daily. Lopinavir/ritonavir administration significantly decreased bupropion and its metabolite's (hydroxybupropion) plasma exposures. This decrease is likely due to the concurrent induction of cytochrome P450 2B6 and UDP-glucuronosyltransferase enzymes. No significant changes in the blood levels of lopinavir or ritonavir were found following administration of a single dose of bupropion. As the maximum recommended dose of bupropion (300 mg per day) should not be increased to compensate for this induction effect, the combination should be avoided. However, if deemed unavoidable, clinical monitoring for lack of bupropion efficacy will be necessary. |
| II/0019 | Update of sections 4.2, 4.4 and 4.5 of the SPC to reflect results from an interaction study evaluating | 26/06/2008 | 26/06/2008 | SmPC and PL | This interaction study, performed in healthy volunteers, had shown that a dose increase to lopinavir/ritonavir |

| | | | | | |
|---|---|---|---|---|---|
| | the co-administration of lopinavir/ritonavir tablets with efavirenz. The PL was updated in accordance.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | 500/125 mg twice daily (two 200/50 mg tablets + one 100/25 mg tablet) co-administered with efavirenz 600 mg every evening (once daily) allowed to achieve adequate lopinavir plasma exposure compared to the standard lopinavir/ritonavir 400/100 mg twice daily regimen administered alone (Cmax +12%, AUC +6%, Ctrough -5%, Cmin -10%). The SPC was updated to reflect this information together with updated specific dosage recommendations for this co-administration. The PL was updated to highlight to patients that they need to consult with their physician if they are taking either efavirenz or nevirapine together with lopinavir/ritonavir. |
| IA/0028 | IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) | 13/06/2008 | n/a | | |
| IA/0027 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 08/05/2008 | n/a | Annex II and PL | |
| II/0018 | Update of sections 4.4 and 5.1 of the SPC with information on the potential for QTc and PR interval prolongation based on the results from a clinical study in healthy volunteers.<br>Furthermore, wording in Annex II was corrected.<br><br>Update of Summary of Product Characteristics | 24/04/2008 | 24/04/2008 | SmPC and Annex II | Based on the results of a study in healthy volunteers which evaluated the potential for ritonavir and lopinavir/ritonavir to induce QTc interval and PR interval prolongation at doses (administered over 3 days) chosen to provide maximal concentrations of both lopinavir and ritonavir, the CHMP concluded that lopinavir/ritonavir has a potential to induce modest QTc and PR interval prolongation. No subject experienced an increase in QTcF of > 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. The mean changes from baseline in PR interval ranged from 11.6 ms to 24.4 ms in the 12 hour interval post dose. Maximum PR interval was 286 msec and no second or third degree heart |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | block was observed. The Product Information was updated in accordance. |
| IB/0023 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 13/02/2008 | n/a | | |
| IB/0022 | IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) | 13/02/2008 | n/a | | |
| IA/0021 | IA_09_Deletion of manufacturing site | 07/02/2008 | n/a | | |
| X/0010 | The SOH applied for an additional strength of 100/25 mg film-coated tablets.<br><br>Annex I_2.(c) Change or addition of a new strength/potency | 24/01/2008 | 24/01/2008 | SmPC, Labelling and PL | In order to offer more options for the treatment of paediatric patients, the SOH applied for an additional strength 100/25 mg film-coated tablets. These tablets have been developed as an alternative to the oral solution and might bring a significant improvement of the dosing management of infants.<br>Aluvia 100/25 mg film coated tablet contains the same active ingredients and excipients in the same proportional amounts as currently the approved Aluvia 200/50 mg with the exception of coating material.<br>Both strengths of the Aluvia tablets are manufactured at the same manufacturing sites, on the same manufacturing lines, using the same manufacturing processes.<br>Bioequivalence data submitted showed that following a single dose of lopinavir/ritonavir 400/100 mg, the new formulation Aluvia 100/25 mg is bioequivalent to the reference formulation Aluvia 200/50 mg. Pharmacokinetic studies were performed on compliance with GLP and GCP. |
| IA/0020 | IA_32_a_Change in batch size of the finished product - up to 10-fold | 17/01/2008 | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| IA/0017 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 14/12/2007 | n/a | | |
| II/0011 | Update of sections 4.3, 4.4 and 4.5 of the SPC based on a comprehensive review of 3 studies examining the pharmacokinetics of co-administered lopinavir/ritonavir and rifampicin as requested by the CHMP in February 2007. The PL was updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 18/10/2007 | 18/10/2007 | SmPC and PL | Following the review of 3 interaction studies with lopinavir/ritonavir and rifampicin, the CHMP considered that an increase dose of Aluvia might allow compensating for the inducer effect of rifampicin, however such an increased dose appeared to be associated with an increased liver toxicity. Therefore, the CHMP considered to revise the Product Information to downgraded the contra-indication concerning rifampicin to a warning and to point out that:<br>- Rifampicin in combination with Aluvia may cause large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect.<br>- Adequate exposure to lopinavir/ritonavir may be achieved when higher dose of Aluvia is used but this is associated with a higher risk of liver and gastrointestinal toxicity.<br>- This co-administration should be avoided unless judged strictly necessary. |
| II/0015 | Update of sections 4.4 and 4.5 of the SPC following the CHMP's assessment of PSUR 9 for Aluvia in May 2007. Consequently, the Package Leaflet is updated.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 20/09/2007 | 20/09/2007 | SmPC and PL | Based on the information considered in the last Periodic Safety Update Report (PSUR), The SOH was requested to include information regarding the potential for drug interactions between lopinavir/ritonavir, Phenytoin, chemotherapeutic agents such as vincristine/vinblastine and rosuvastatin. A review of cases and literature for these potential interactions of co-administration with lopinavir/ritonavir indicated scientific evidence for:<br><br>- Increased concentrations of vincristine/vinblastin, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | - Decreases in both phenytoin and lopinavir/ritonavir exposure,<br>- Increases in rosuvastatin exposure.<br><br>The CHMP agreed to update the Product Information to reflect these findings. |
| II/0013 | Update of section 4.5 of the SPC with information available in the public domain on the interaction of buprenorphine and lopinavir/ritonavir following the CHMP's request on 26 April 2007.<br><br>Update of Summary of Product Characteristics | 20/09/2007 | 20/09/2007 | SmPC | A recent interaction study between buprenorphine and lopinavir/ritonavir, available in the public domain (McCance-Katz et al., 2006), showed that the co-administration of both medicines at normal therapeutic doses did not lead to a significant changes in blood levels of buprenorphine and its metabolites or lopinavir/ritonavir. Based on these data, co-administration of lopinavir/ritonavir and buprenorphine is well tolerated and does not result in clinically significant drug interactions which would require altering of dosing recommendations. The SPC was updated to reflect this finding accordingly. |
| IA/0016 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 23/08/2007 | n/a | | |
| IB/0014 | IB_10_Minor change in the manufacturing process of the active substance | 13/08/2007 | n/a | | |
| II/0009 | Update of sections 4.3 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.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 21/06/2007 | 21/06/2007 | SmPC and PL | A phenotyping cocktail study investigating the co-administration of midazolam with fixed combination lopinavir/ritonavir in 14 healthy volunteers showed an increase of midazolam AUC by about 13 fold when midazolam was given orally and an increase by about 4 fold when midazolam was given parenterally. Therefore, the co-administration of lopinavir/ritonavir with orally |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | administered midazolam is contraindicated, whereas caution should be used when lopinavir/ritonavir is co-administrated with injection of midazolam.<br>If lopinavir/ritonavir 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.<br>Sections 4.3 and 4.5 of the SPC and section 2 of the PL are updated with this information. |
| IA/0012 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 20/06/2007 | n/a | | |
| IB/0008 | IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) | 16/05/2007 | n/a | | |
| II/0002 | Update of section 4.5 of the SPC based on an interaction study between lopinavir/ritonavir and stomach acid reducing agents (omeprazole or ranitidine). Consequentially, the Package Leaflet was updated as well.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 22/02/2007 | 22/02/2007 | SmPC and PL | The study, which was conducted in healthy volunteers, showed that after administration of multiple oral doses of the currently approved therapeutic regimen (lopinavir/ritonavir 400/100 mg twice daily) no clinically significant drug-drug interaction between either omeprazole or ranitidine was observed. The results were in accordance with the pH-solubility profiles of lopinavir and ritonavir and with the physico-chemical mechanism involved in the drug-drug interaction between protease inhibitors and acid-reducing agents related to a decreased solubility of the molecule with increasing pH. As this co-administration is frequent in clinical practice and therefore of practical relevance to the prescribers, the results from this |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | interaction study were included in the SPC and PL. |
| II/0001 | Update of sections 4.8 and 5.1 of the SPC to reflect the long-term (7 year) safety and efficacy data now available from a phase I/II study in antiretroviral naïve patients, the PL is updated as well.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 22/02/2007 | 22/02/2007 | SmPC and PL | The submitted data demonstrate long term durability of lopinavir/ritonavir in the treatment of antiretroviral naïve HIV-1 infected patients. The study was originally designed as a dose selection study and consequently, the study population is small. This limits the evaluation of the provided data. Nevertheless, Week 360 results of the study show that lopinavir/ritonavir is safe while maintaining antiretroviral efficacy, with 61% and 59% of antiretroviral naïve patients initially enrolled demonstrating plasma HIV-1 RNA levels < 400 copies/ml and < 50 copies/ml, respectively. The safety profile of lopinavir/ritonavir remains essentially unchanged, as the reported adverse events did not show new or major issues. However, based on the analysis of the updated information about adverse events reported within this study, the frequency categorise for pain, acne and paresthesia were changed from uncommon to common. |
| II/0006 | Update of section 5.1of the SPC to include recommendations on the therapeutic options in case of virological failure. To this purpose, the information in the cross-resistance sub-section is updated with new information.<br><br>Update of Summary of Product Characteristics | 24/01/2007 | 24/01/2007 | SmPC | Based on the in vitro data presented on cross-resistance of lopinavir with other protease inhibitors, tipranavir could be a suitable option for salvage therapy to Aluvia, provided that the viral strains do not harbour the pejorative mutations for clinical response to tipranavir (three or more mutations at positions 33, 82, 84 or 90). The cross-resistance subsection was therefore reworded to reflect these findings.<br>Furthermore, the resistance section was re-structured and updated with information on in vitro data in antiretroviral naïve and experienced patients. |

| | | | | | |
|---|---|---|---|---|---|
| II/0005 | To update sections 4.3, 4.4, 4.5 and 4.8 of the SPC with new safety information. Changes include the addition of potential interactions with digoxin, fosamprenavir, tadalafil, vardenafil, trazodone, tenofovir and voriconazole, the addition of patch contraceptives and information about serious skin reactions. Consequentially, sections 2 and 4 of the PL are updated. Section 4 of the PL is also updated to include a comprehensive list of all other common and uncommon side effects.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/01/2007 | 24/01/2007 | SmPC and PL | Further to the assessment of the lopinavir/ritonavir PSURs 6 and 7 (1.10.03 - 30.9.04) and to a safety review, the information of Aluvia was updated in regard to new information about potential interactions with digoxin, fosamprenavir, tadalafil, vardenafil, trazodone, tenofovir and voriconazole. Additinally, information about patch contraceptives completed the existing information on interactions between lopinavir/ritonavir and contraceptive medicinal products based on hormone derivatives. Erythrema mulitforme and Stevens-Johnson syndrome were added to the undesirable effects based on post-marketing experience observed with the use of lopinavir/ritonavir. |
| II/0007 | Update of section 4.4 and section 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.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 14/12/2006 | 14/12/2006 | SmPC and 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 multi 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. |
| IB/0004 | IB_10_Minor change in the manufacturing process of the active substance | 14/11/2006 | n/a | | |

| | | | | | |
|---|---|---|---|---|---|
| IA/0003 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 17/10/2006 | n/a | | |