EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Viracept

Procedural steps taken and scientific information after the authorisation

Changes made after 1 May 2004

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

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
II/0122	Update of sections 4.3, 4.4 and 4.5 of the SmPC to upgrade the warning on co-administration with lovastatin and simvastatin to a contraindication and to include a general warning that statins may interact with protease inhibitors and should be used with caution. The Package Leaflet was updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical o	24/05/2012	27/06/2012	SPC, PL	Based on available safety data related to interactions between protease inhibitors and statins the CHMP recommended the upgrade of the warning about concomitant use of simvastatin and lovastatin to a contraindication, together with consequent changes to other sections of the SmPC and PL. The product information was also updated to reflect that other statins may also interact with protease inhibitors and should be used with caution since this could increase the risk of myopathy, including rhabdomyolysis.

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

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	pharmacovigilance data				
N/0121	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/03/2012	n/a	PL	
II/0119	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	05/09/2011	SPC, Annex II, PL	
II/0120	To update sections 4.3, 4.4 and 4.5 of the SmPC regarding interactions with warfarin, PDE-5 inhibitors for pulmonary arterial hypertension and erectile dysfunction, colchicine, alfuzosin, salmeterol and bosentan as per CHMP request. The package leaflet has been revised accordingly. In addition, minor changes have been made in accordance with the QRD template and for consistency throughout the product information. Finally, the MAH has taken the opportunity to update Annex IIIA to include changes according to their new packaging design. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	27/05/2011	SPC, Annex II, Labelling, PL	Nelfinavir is metabolised by multiple cytochrome P-450 enzymes including CYP3A4 and CYP2C19 with known inhibitory effects on CYP3A4. Some data suggest that nelfinavir may also induce CYP2C9. Therefore the product information of nelfinavir has been revised to reflect pharmacokinetic interactions with the following medicinal products: warfarin, PDE-5 inhibitors, colchicine, alfuzosin, salmeterol and bosentan. Theoretically, an induction and/or an inhibitory effect of nelfinavir on warfarin metabolism could be expected, as nelfinavir is an inducer and warfarin is a substrate of CYP2C9 and nelfinavir is also an inhibitor of CYP3A4, while warfarin is a substrate of this enzyme. Therefore, information regarding possible interaction with warfarin has been included in section 4.5 of the SmPC of nelfinavir and in the package leaflet accordingly. PDE5 inhibitors (sildenafil, tadalafil and vardenafil) are metabolised by CYP3A4. Therefore, information on pharmacokinetic interactions with PDE5 inhibitors has been reflected in section 4.5. Co-administration of Viracept with these medicinal products is expected to increase their concentrations and may result in associated adverse events such as hypotension, syncope, visual changes and prolonged erection. A class warning has been included in section 4.4 of the SmPC. In addition, concomitant use of sildenafil prescribed for the treatment of pulmonary arterial hypertension with Viracept is contraindicated in line with the recommendations made for other HIV protease inhibitors and the section 4.3 has been updated accordingly. Similarly, precautions regarding concomitant administration of colchicine in patients with renal or hepatic impairment, concomitant administration with salmeterol, or concomitant

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					administration with bosentan have been included in the product information due to pharmacokinetic interactions. Finally, concomitant use of alfuzosin (an alpha blocker indicated for the treatment for benign prostatic hyperplasia)
II/0116	Update of sections 4.2, 4.5 and 5.2 of the SmPC following the CHMP's assessment of PSUR 13 on 21 August 2008. In addition and as requested by the CHMP, the MAH reviewed some inconsistencies between the Annexes of the different pharmaceutical forms of nelfinavir. Consequently, section 2 of the PL was updated. The MAH also took this opportunity to update the PL with the results of the user testing Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	20/01/2010	SPC, PL	The MAH searched its post-marketing database for any significant issues regarding the interaction of statins and nelfinavir. Considering the lack of relevant new information emerging from this review, it was agreed that the warning and recommendations with regards to this interaction as presented in section 4.5 of the SmPC is sufficient. Further updates included a clearer presentation of the posology in children in section 4.2 and the tabular presentation of pharmacokinetic results of studies done in both children as well as patients with hepatic impairment in section 5.2. The PL was updated with the results of the user testing, which has led to a presentation of information on Viracept in a much more accessible way for patients.
IB/0118	25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	07/07/2009	n/a		
IB/0117	19_b_Change in specification of an excipient - addition of new test parameter	28/01/2009	n/a		
IA/0114	08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	30/07/2008	n/a	Annex II, PL	
II/0112	Update of sections 4.3, 4.4, 4.8, 5.1 and 5.2 of the SPC as well as the PL in line the CHMP's request in the framework of the renewal assessment in November 2007. In addition, the MAH took this opportunity to update section 4.5 of the SPC in line with the new template A of the updated HIV guideline. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	28/07/2008	SPC, PL	This update has clarified the SPC and therefore improved it consistently. A wording is introduced in section 4.3 regarding potential association with potent inducers of CYP3A4. The introduction of a tabulated format for the interaction section makes the presented information much more accessible to the treating physician and was therefore endorsed by the CHMP. Furthermore, changes to the PL have considerably improved its readability.
II/0111	Update of section 4.8 of the SPC and section 4 of the PL with safety information on	24/04/2008	20/06/2008	SPC, PL	Further to the assessment of PSUR 12 in August 2007 the MAH was requested to present a cumulative review with all available

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	paediatric population, as requested by the CHMP following the assessment of PSUR 12 in August 2007. Update of Summary of Product Characteristics and Package Leaflet				information (spontaneous reports, clinical studies and published literature) to determine what adverse reactions are experienced by infants exposed to nelfinavir in utero and by children. Approximately 400 children and neonate received nelfinavir in four clinical studies for up to 96 weeks. The most common adverse event was diarrhoea. Neutropenia/leukopenia was the laboratory abnormality most frequently reported. In spontaneous reports, hypertriglyceridemia, anaemia, blood lactic increased and pneumonia were also reported however, the frequency of ocurrence could not be determined.
II/0110	Update of or change(s) to the pharmaceutical documentation	24/01/2008	30/01/2008		
R/0108	Renewal of the marketing authorisation	15/11/2007	10/01/2008	SPC, Annex II, Labelling, PL	
II/0106	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. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	19/10/2007	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 Viracept with orally administered midazolam is contraindicated, whereas caution should be used when Viracept is co-administrated with injection of midazolam. If Viracept 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 and 4.5 of the SPC and section 2 of the PL are updated with this information.
II/0105	Update of sections 4.3, 4.4 and 4.5 of the SPC based on an interaction study evaluating the effects of multiple doses of omeprazole on the steady-state pharmacokinetics of nelfinavir and its major metabolite, M8. Consequently, the PL is updated. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	19/10/2007	SPC, PL	The results of the interaction study showed that the co-administration of omeprazole and Viracept leads to significantly lower blood levels of both nelfinavir and its main active metabolite M8. This interaction was shown in healthy volunteers, receiving the currently approved dosage regimens for both nelfinavir and omeprazole at steady-state. As the lowered blood levels of nelfinavir could lead to sub-optimal efficacy of this medicine, i.e. lack of suppression of virus replication, the CHMP decided to contraindicate this co-administration. Furthermore, due to the possible underlying mechanisms of this interaction, a

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					precaution against the use of any medicines affecting gastric pH was added as well.
Z/0109	(Review of) Suspension	20/09/2007	15/10/2007		For further information please refer to the scientific conclusions: Viracept-H-164-Z-109
A20/0107	Article 20 Review	21/06/2007	06/08/2007		For further information please refer to the scientific conclusions: Viracept-H-164-A20-107
IA/0104	05_Change in the name and/or address of a manufacturer of the finished product	27/04/2007	n/a	SPC, Annex II, PL	
II/0103	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. Section 6 of the PL was updated with the local representatives in Bulgaria and Romania. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	11/01/2007	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 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.
IA/0102	47_b_Deletion of a strength	23/10/2006	n/a	SPC, Labelling, PL	
IB/0100	29_a_Change in qual./quant. composition of immediate packaging - semi-solid/liquid ph. forms	06/06/2006	n/a	SPC	
II/0097	Update of section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to include results from two comparator studies (lopinavir/ritonavir versus Viracept) and (fosamprenavir/ritonavir versus Viracept) to adequately reflect the results of these pivotal clinical studies where Viracept was used as the comparator protease inhibitor. In addition, section 4.2 "Posology and	26/01/2006	28/02/2006	SPC, PL	Based on data presented from two comparator studies (Kaletra vs. Viracept and Telzir/ritonavir vs. Viracept), the pharmacodynamic data in the SPC of Viracept was amended to include the results of these studies as they have an impact on the choice of the first-line antiretroviral regimen by the treating physician. The advantage of relative low treatment-emergent PI cross-resistance which is offset by the significantly higher rate of treatment-emergent NRTI resistance after therapy failure with nelfinavir is mentioned. Furthermore, the relatively unfavourable efficacy profile of nelfinavir when compared to the two ritonavir-

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	Method of Administration" of the SPC and section 3 "How to take Viracept" of the PL of the Viracept powder formulation are revised to increase the intelegibility of the existing dosing regimen. Update of Summary of Product Characteristics and Package Leaflet				boosted PI regimens is highlighted. However, Viracept may still be the PI of choice when the concomitant use of ritonavir is not possible, when a relatively less hepatotoxic agent is needed and to avoid in utero transmission during pregnancy.
IB/0099	12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	19/12/2005	n/a		
IA/0098	01_Change in the name and/or address of the marketing authorisation holder	25/10/2005	n/a	SPC, Labelling, PL	
IA/0096	09_Deletion of manufacturing site	22/07/2005	n/a		
II/0095	To update the SPC, section 4.8 to include erythema multiforme as a very rare adverse drug reaction, following a request made during the assessment of the 9th PSUR, covering the period from 1 April 2003 to 31 March 2004. The Product Information of the oral powder formulation, the 250 mg uncoated and coated tablet formulations are brought in line with the Product Information of the latest approved 625 mg formulation, and in addition, information on lactation is harmonised for all formulations. Minor modifications are made in the SPC, Annex II and in the labelling in accordance with the latest EMEA/QRD templates. Finally, in the PL, the list of local representatives has been updated. Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/04/2005	10/06/2005	SPC, Annex II, Labelling, PL	The safety database was analysed for cases of serious skin reactions associated with Viracept. A total of 75 cases reported epidermal necrolysis, erythema multiforme, rash maculopapular or Stevens Johnson Syndrome were identified. Causal relationship was assessed. Based on the review, the MAH proposes to add erythema multiforme to section 4.8 of the SPC. The MAH has estimated the frequency to be very rare. In addition, the MAH has updated the SPCs in line with the information on the 625 mg tablets. Finally, SPC and PL of the different formulations were harmonised with regard to the use of Viracept during lactation.
II/0094	To update section 4.4 and 4.8 of the SPC and section 2 of the PL to implement the	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

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	class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Update of Summary of Product Characteristics and Package Leaflet				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.
II/0093	To update section 5.3 of the SPC with data from the final study report on mouse carcinogenicity. In addition, the list of representatives in the PL is amended to include all current Member States. Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	20/10/2004	SPC, PL	In a mouse carcinogenicity study, nelfinavir mesylate or control preparations were administered by oral gavage to groups of CD-1 mice at doses of 0, 125, 250, 500 and 1000 mg /kg/day for up to 104 weeks. A further group was untreated. 60 males and females were assigned to each treatment group for the carcinogenicity investigation. Additional animals were assigned to a toxicokinetic investigation; some of these were added to the carcinogenicity study, increasing the number of animal/sex from 60 to 70 in the vehicle group and from 60 to 84 in the nelfinavir groups. A premature loss of all animal of the two high groups was observed which was attributed to inadvertent disposition of drug suspension in the back of the nasopharyngeal cavity, resulting in plugs. However, as this study included four treatment groups instead of the conventional three, this finding has not prejudiced the evaluation of the cacinogenic potential; at least 26 animals

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					of each sex survived to study termination in the two control and the 125 and 250 mg/kg/day nelfinavir groups. There was no evidence of oncogenic potential.