The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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EMEA PUBLIC STATEMENT ON THE RISK OF DRUG INTERACTIONS WITH *HYPERICUM PERFORATUM* (ST JOHN'S WORT) AND ANTIRETROVIRAL MEDICINAL PRODUCTS

The European Medicines Evaluation Agency (EMEA) would like to draw attention to the fact that products containing *Hypericum perforatum* (**St John's wort)** have the potential to interact with medicinal products. *Hypericum perforatum* is widely used in different products that can either be freely sold or made available subject to medical prescription.

During the last year, information on drug interactions between *Hypericum perforatum* and medicinal products, including cyclosporin, digoxin, oral contraceptives, theophylline and warfarin, has become available either as case reports or as pharmacokinetic data. These interactions are most likely related to the induction of certain isoenzymes of the cytochrome P450 system by *Hypericum perforatum*. These interactions may lead to a reduction in plasma concentrations and hence reduction of the therapeutic effect of these medicinal products. Because these interactions are caused by enzyme induction, stopping herbal products containing *Hypericum perforatum* may also lead to increased blood levels of some medicines resulting in toxicity (particularly cyclosporin, digoxin, theophylline and warfarin).

Recent information included the results of an interaction study performed by The National Institutes of Health (United States) between *Hypericum perforatum* and indinavir **(Crixivan)**[1], a protease inhibitor indicated for the treatment of HIV-1 infected adult patients. The study, which was carried out in healthy volunteers, showed that when co-administered *Hypericum perforatum* significantly reduced the indinavir plasma concentrations. This interaction is likely to be related to the induction of isoenzyme 3A4 of the cytochrome P450. These results may have important clinical implications for HIV-1 infected patients since sub-therapeutic plasma concentrations of indinavir can lead to the development of resistance and treatment failure.

There is currently no information as to whether this interaction also occurs with other antiretroviral medicinal products. Considering the metabolism and elimination pathways of these antiretroviral medicinal products particularly protease inhibitors and non-nucleoside reverse transcriptase inhibitors, there is a potential risk of interaction when they are co-administered with *Hypericum perforatum* and hence decrease in therapeutic effect. The list of centrally authorised antiretroviral medicinal products is attached for information. In addition there are other nationally authorised antiretroviral medicinal products containing zidovudine, didanosine and zalcitabine.

[1] The Lancet, vol 355 – February 12, 2000 p 547-548

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Until more detailed information is available, potential interactions between *Hypericum perforatum* and other medicinal products metabolised by certain isoenzymes of the cytochrome P450 system are likely to occur.

Following review by the EMEA's scientific committee, the Committee for Proprietary Medicinal Products (CPMP), the EMEA makes the following recommendations:

- **Patients treated with indinavir and, by extrapolation also other antiretroviral medicinal products for the treatment of HIV-1 infection, should not take products containing *Hypericum perforatum* as this may result in loss of therapeutic effect and development of resistance.**

- **For patients treated with other medicinal products and taking products containing *Hypericum perforatum* or who have the intention to do so, further advice will be issued to health care professionals and to patients by National Competent Authorities, taking into consideration the local regulatory status of these products.**

Health care professionals are encouraged to ask patients about use of products containing *Hypericum perforatum* and to report suspected interactions between *Hypericum perforatum* and any medicinal products to the national adverse reaction reporting schemes.

Furthermore, the CPMP will continue to assess evidence on this issue and will request amendments to the Summary of Product Characteristics and Package Leaflet of the centrally authorised medicinal products accordingly.

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Annex 1
Antiretroviral medicinal products centrally authorised within the European Union

Class	Trade name	International non-proprietary name	Marketing Authorisation Holder
Protease inhibitors	Crixivan	Indinavir	Merck Sharp & Dohme Limited
	Fortovase	Saquinavir	Roche Registration Limited
	Invirase	Saquinavir	Roche Registration Limited
	Norvir	Ritonavir	Abbott Laboratories Limited
	Viracept	Nelfinavir	Roche Registration Limited
Non-nucleoside reverse transcriptase inhibitors	Stocrin	Efavirenz	Merck Sharp & Dohme Limited
	Sustiva	Efavirenz	DuPont Pharmaceuticals Limited
	Viramune	Nevirapine	Boehringer Ingelheim International GmbH
Nucleoside reverse transcriptase inhibitors	Combivir	Lamivudine/zidovudine	Glaxo Group Limited
	Epivir	Lamivudine	Glaxo Group Limited
	Zerit	Stavudine	Bristol-Myers Squibb Pharma EEIG
	Ziagen	Abacavir	Glaxo Group Limited