



European Medicines Agency  
Press office

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### **EMEA PUBLIC STATEMENT**

#### **Important new pharmacokinetic data demonstrating that REYATAZ (atazanavir sulfate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered**

The European Medicines Agency (EMA) and its scientific Committee (CHMP) have been made aware of important new pharmacokinetic (PK) data concerning the coadministration of REYATAZ (atazanavir sulfate) combined with ritonavir (RTV) and 40 mg omeprazole, a proton pump inhibitor.

The following observations were made from a randomized, open-label, multiple-dose drug interaction study performed in healthy volunteers (*see annex 1 for details of the study*):

A 76% reduction in atazanavir area under the concentration-time curve (AUC) and a 78% reduction in atazanavir trough plasma concentration (C<sub>min</sub>) were observed when REYATAZ/RTV (300/100 mg) was co-administered with omeprazole 40 mg. The exact mechanism is currently unknown. It could be the result of an alteration of the gastric pH induced by omeprazole which is known to influence REYATAZ absorption, but other mechanisms such as cytochrome-mediated mechanism cannot be ruled out.

#### **The EMA wishes to point out the following important safety information to physicians:**

Based on the study results:

- DO NOT coadminister REYATAZ/RTV 300/100 mg with omeprazole due to the reduction in REYATAZ exposure levels.
- In this study, an omeprazole dose of 40 mg was used. It is not known whether other daily doses would produce similar results and, therefore, coadministration of any doses of omeprazole IS NOT recommended.
- Increasing the REYATAZ/RTV dose to 400/100 mg in combination with omeprazole DID NOT result in REYATAZ exposure levels comparable to those observed with a regimen of REYATAZ/RTV 300/100 mg without omeprazole.
- In the absence of any data with other proton pump inhibitors, the recommendations should be extended to the whole class of proton pump inhibitors.

Moreover, investigations regarding the potential drug interaction between REYATAZ and H<sub>2</sub>-Receptor antagonists when co-administered are ongoing. Until data are available, and as currently recommended in the REYATAZ SPC, caution should be exercised when these drugs are co-administered.

#### **Information for patients:**

Reyataz and Norvir should not be given together with proton pump inhibitors (e.g. omeprazole), a class of medicines used to treat excess acid in the stomach and heartburn. Giving these medicines together can reduce the effect of Reyataz/Norvir. Should you be receiving such combination, you need to discuss your treatment with your doctor.

The Summary of Product Characteristics and Patient Information Leaflet are currently being revised to take into account this new information.

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## Note for editors

REYATAZ is an azapeptide HIV-1 protease inhibitor. It is indicated for the treatment of HIV-1 infected, antiretroviral treatment experienced adults, in combination with other antiretroviral medicinal products. Ritonavir is used as a booster of atazanavir pharmacokinetics. Atazanavir was first approved in European countries on 02 March 2004 under exceptional circumstances\*. Within the EU, it is marketed as hard capsules and powder for oral use.

\* Marketing Authorisation under exceptional circumstances refers to the fact that in exceptional circumstances an authorisation may be granted subject to certain specific obligations, to be reviewed annually.

## Annex 1

### Description of the study results:

This study was a randomized, open-label, multiple-dose drug interaction study performed in healthy subjects and aimed at assessing comparability of the steady-state pharmacokinetics of:

- Omeprazole 40mg orally OAD + ATV 300mg orally OAD and RTV 100mg orally OAD for 10 days (n=15)
- Omeprazole 40mg orally OAD + ATV 300mg orally OAD with 8 ounces of cola and RTV 100mg orally OAD for 10 days (n=15)  
*The co-administration with cola was made to explore whether its acidity could compensate for the antacid effect of omeprazole on atazanavir pharmacokinetics.*
- Omeprazole 40mg orally OAD + ATV 400mg orally OAD and RTV 100mg orally OAD for 10 days (n=14)

In all cases, REYATAZ/RTV was administered with a light meal, and omeprazole was administered on an empty stomach 2 hours prior to REYATAZ/RTV. Subjects in each treatment arm received REYATAZ/RTV (300/100 mg) for 10 days prior to randomisation.

**Pharmacokinetic Parameters for REYATAZ** (Geometric Mean Ratios [90% confidence interval] and % Reduction as compared to REYATAZ/RTV 300/100 mg alone) are detailed in the table below :

Pharmacokinetic Parameter	ATV/RTV 300/100		
	ATV/RTV 300/100 mg + omeprazole 40 mg once daily	mg + omeprazole 40 mg + 8 oz of cola once daily	ATV/RTV 400/100 mg + omeprazole 40 mg once daily
$C_{max}$ (ng/mL)	0.279 (0.242, 0.321)	0.337 (0.293, 0.388)	0.437 (0.378, 0.506)
% Reduction in $C_{max}$	72	66	56
AUC(TAU) (ng*hr/mL)	0.240 (0.211, 0.274)	0.301 (0.265, 0.343)	0.394 (0.345, 0.451)
% Reduction in AUC	76	70	61
$C_{min}$ (ng/mL)	0.223 (0.188, 0.264)	0.271 (0.228, 0.321)	0.345 (0.289, 0.411)
% Reduction in $C_{min}$	78	73	66

\* ATV = atazanavir, RTV = ritonavir,  $C_{max}$  = peak plasma concentration, AUC(TAU) = area under the plasma concentration-time curve in one dosing interval,  $C_{min}$  = trough plasma concentration

Omeprazole exposures were generally comparable to literature values, and individual subject exposures overlapped across treatments.