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Questions and answers on drug interactions between Victrelis (boceprevir) and ritonavir-boosted HIV protease inhibitors

The European Medicines Agency has recommended changes to the prescribing information for Victrelis (boceprevir), a medicine used to treat hepatitis C, after a drug interaction study identified interactions between Victrelis and medicines used to treat HIV called ritonavir-boosted HIV protease inhibitors. These interactions could potentially reduce the effectiveness of these medicines if used together in patients being treated for both hepatitis C and HIV. The Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended the changes to ensure doctors are informed of these interactions while further data are awaited to assess the clinical impact of these drug interaction findings on these patients.

What is Victrelis?

Victrelis is a medicine used to treat long-term hepatitis C genotype 1 (a disease of the liver due to infection with the hepatitis C virus) in adults with compensated liver disease who have not been treated before or whose previous treatment has failed. Compensated liver disease is when the liver is damaged but is still able to work normally. Victrelis is given in combination with two other medicines, peginterferon alfa and ribavirin.

The active substance in Victrelis, boceprevir, is a protease inhibitor which blocks an enzyme called HCV NS3 protease found on the hepatitis C genotype 1 virus.

Victrelis was authorised in the EU in July 2011.

What is the issue with Victrelis?

In January 2012, the EMA was informed of the results of a study in healthy volunteers which identified drug interactions between Victrelis and the antiviral medicines atazanavir, darunavir and lopinavir, which are used to treat HIV. These medicines are given with ritonavir, another antiviral medicine, to boost their concentrations. They are collectively known as 'ritonavir-boosted HIV protease inhibitors'.

The study was carried out by the marketing authorisation holder for Victrelis, Merck Sharp & Dohme Ltd, following a request from the CHMP. At the time of the marketing authorisation for Victrelis, the results of a drug interaction study between ritonavir and Victrelis were available which did not show any significant interaction. Based on this, significant interactions were not expected with ritonavir-

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

boosted HIV protease inhibitors but specific data with ritonavir-boosted HIV protease inhibitors was requested to further assess this issue.

The new findings may be significant due to the size of the effect seen as the interactions could potentially reduce the effectiveness of these medicines if they are used together in patients treated for hepatitis C and HIV, since many patients are co-infected with hepatitis C virus and HIV.

Which data has the CHMP reviewed?

The CHMP reviewed the data from the drug interaction study in 39 healthy volunteers between Victrelis and ritonavir-boosted HIV protease inhibitors, which looked at the levels of the medicines in the recipients' blood. The Committee also looked at preliminary results from an ongoing study involving 100 patients co-infected with hepatitis C virus and HIV, where most patients were given Victrelis together with ritonavir-boosted HIV protease inhibitors.

What are the conclusions of the CHMP?

The drug interaction study in healthy patients found that blood levels of all three HIV medicines were markedly lower than expected when given with Victrelis. It also found that blood levels of Victrelis were markedly lower than expected when given with ritonavir-boosted darunavir or lopinavir, although this effect was not seen with ritonavir-boosted atazanavir. The CHMP concluded that the lower blood levels seen could mean that the medicines may be less effective when given together to patients co-infected with HIV and hepatitis C virus.

The CHMP considered that firm conclusions could not be drawn from the preliminary results of the ongoing study in co-infected patients. The Committee agreed that further clinical data from studies in co-infected patients will allow the clinical impact on these patients to be assessed, including the final results of this ongoing study and a study conducted by the French national agency for research on AIDS[1] (including patients receiving atazanavir/ritonavir).

While awaiting this further information, the Committee considered that the product information for Victrelis should be updated to include the new data from the drug interaction study, with recommendations on the co-administration of Victrelis with the different ritonavir-boosted HIV protease inhibitors. The product information will also state that clinical studies are ongoing in co-infected patients treated with Victrelis and HIV protease inhibitors.

The Committee has agreed with the company on a letter to be sent out to healthcare professionals in the EU, informing them of the CHMP's recommendations based on the new drug interaction data and notifying them that further data is awaited from ongoing clinical studies in co-infected patients.

The full changes made to the information to doctors and patients are detailed here.

What are the recommendations for prescribers?

- Doctors treating patients for hepatitis C and HIV should be aware that concentrations of ritonavir-boosted HIV protease inhibitors are reduced when given with Victrelis, which could reduce their effectiveness. Concentrations of Victrelis are reduced when given with ritonavir-boosted darunavir or lopinavir, which could reduce its effectiveness.
- Doctors should not co-administer Victrelis with ritonavir-boosted darunavir or lopinavir. Co-administration with ritonavir-boosted atazanavir may be considered on a case-by-case basis if

[1] *Agence nationale de recherche sur le SIDA et les hépatites virales* (ANRS).

deemed necessary in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted.

- Doctors should discuss these findings with patients currently being treated with HIV protease inhibitors and Victrelis, and should closely monitor how these patients respond to both treatments.

What are the recommendations for patients?

- Patients who are currently receiving treatment for HIV and hepatitis C should discuss their ongoing treatment with their doctor at the next scheduled appointment.
- Patients should not stop taking any of their medicines without talking to their doctor.
- Patients who have any questions should speak to their doctor or pharmacist.

A European Commission decision on this opinion will be issued in due course.