21 November 2013
EMA/CHMP/40711/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aptivus

International non-proprietary name: TIPRANAVIR

Procedure No. EMEA/H/C/000631/II/0060

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 23 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Aptivus	TIPRANAVIR	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	II

The MAH proposed the update of sections 4.3 and 4.5 of the SmPC to include information regarding quetiapine following a class labelling for all HIV protease inhibitors. The Package Leaflet was proposed to be updated accordingly.

In addition, the MAH took the opportunity to add Croatia to the list of local representatives in the Package Leaflet.

Furthermore, minor linguistic changes (linguistic corrections) will be proposed to the German/Austrian, Italian, Spanish product information

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Joseph Emmerich

1.2. Steps taken for the assessment

Submission date:	23 August 2013
Start of procedure:	22 September 2013
Rapporteur's preliminary assessment report circulated on:	29 October 2013
CHMP opinion:	21 November 2013

2. Scientific discussion

2.1. Introduction

Aptivus, tipranavir, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older with virus resistant to multiple protease inhibitors. Aptivus should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options.

This indication is based on the results of two phase III studies, performed in highly pre-treated adult patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors and of one phase II study investigating pharmacokinetics, safety and efficacy of Aptivus in mostly treatment-experienced adolescent patients aged 12 to 18 years.

Background on this application: Signal review during the July 2013 PRAC meeting

Lopinavir and ritonavir are protease inhibitors used in the treatment of human-immunodeficiency virus type I (HIV-1) infection.

A signal of an interaction between lopinavir/ritonavir and quetiapine leading to major sedation was identified by France, based on one case described in a scientific conference in France (Peytavin G. Clinical case #1: drug interaction and post-exposure prophylaxis (PEP) for HIV, 7eme Workshop Nouvelles molecules et strategies antiretrovirales.2013;NA:1-43). The Rapporteur for this product confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion during the July 2013 PRAC meeting

During its July 2013 plenary, the PRAC noted the case report of major sedation leading to deep coma in a patient receiving quetiapine and treated with lopinavir / ritonavir used in combination with emtricitabine / tenofovir in the context of HIV post-exposure prophylaxis.

The concomitant administration of HIV protease inhibitors is explicitly contra-indicated in the product information of quetiapine-containing medicinal products due to the risk of increased quetiapine exposure. In contrast, the same contraindication is not reported in the product information of lopinavir/ritonavir-containing medicines although it is stated that medicinal products highly dependent on cytochrome P450 3A (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events should not be co-administered with quetiapine.

Such drug-drug interaction is considered to be due to an increased exposure to quetiapine caused by inhibition of CYP3A4 by lopinavir and ritonavir.

The PRAC agreed that information on the interaction and a contraindication should be included in the product information for lopinavir/ritonavir-containing products, but should also be introduced in the product information of all other protease inhibitor-containing medicines.

Summary of the recommendations adopted by the PRAC in July 2013

- The MAH for Kaletra (lopinavir / ritonavir) should submit to the EMA, within 30 days, a variation with a proposal for amending the product information6 to include a contraindication for the concomitant use of quetiapine.
- The MAHs of all other protease inhibitor-containing medicinal products (ATC code J05AE) should also introduce a contraindication in the product information for these medicines, by appropriate procedures, within 30 days.

A standard wording was agreed by the PRAC for the Summary of Product Characteristics (SmPC) and the Patient Leaflet (PL) of the protease inhibitor-containing medicinal products (ATC code J05AE). The MAH proposed an alternative wording for implementation in the Summary of Product Characteristics (SmPC) for tipranavir and submitted the present application.

The PRAC recommendations were endorsed by the CHMP on 25 July 2013.

2.2. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

SmPC

The MAH proposed to revise and enrich the statements recommended by PRAC in two sections of the SmPC, 4.3 Contraindications and 4.5 Interactions with other medicinal product and other forms of interactions:

In section 4.3 some neuroleptic agents were already listed to be contraindicated. Neuroleptics are synonymously used for antipsychotics. Since the standard term is 'antipsychotics' according to the WHO ATC/DDD index (reference), the MAH suggested replacing the term 'neuroleptics' by 'antipsychotics'. Quetiapine will be therefore listed together with the other antipsychotics.

For clarity and consistency and to heighten the reader's awareness, the MAH suggested the following additional changes and amendments to section 4.3 Contraindications. These additional changes were accepted by the CHMP.

Section 4.3 Contraindications

Co-administration of Aptivus with low dose ritonavir, with active substances that are highly dependent on CYP3A for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events, is contraindicated. These active substances include antiarrhythmics (such as amiodarone, bepridil, quinidine), antihistamines (such as astemizole, terfenadine), ergot derivatives (such as dihydroergotamine, ergonovine, ergotamine, methylergonovine), gastrointestinal motility agents (such as cisapride), ~~neuroleptics~~ antipsychotics (such as pimozide, sertindole, quetiapine), sedatives/hypnotics (such as orally administered midazolam and triazolam~~. For caution on parenterally administered midazolam see section 4.5~~) and HMG-CoA reductase inhibitors (such as simvastatin and lovastatin) (see section 4.5). Also contraindicated is the use of the alpha-1

- Information on parenteral midazolam administration is correctly included in section 4.5 and should be deleted in the contraindication section '*For caution on parenterally administered midazolam see section 4.5*'
- The cross reference from the contraindication section to warnings and precautions '(see section 4.5)' has been moved to the end of the listing of the active substances, as it applies to all listed substances.
- The wording 'such as' has been included in front of the listed active substances in parentheses, since the listed ones are only examples.

Section 4.5 "Interaction with other medicinal products and other forms of interaction"

In Section 4.5 "*Interaction with other medicinal products and other forms of interaction*", the aforementioned amendment was adapted to include the quetiapine information in the pre-existing drug-drug interaction information on 'neuroleptics' which has been replaced by the term 'antipsychotics' due to above mentioned reason. In order to comply with the PRAC's recommendation, the MAH suggested adding 'including coma' after 'serious and/or life-threatening events', to specifically show that the side effects of overdose for all above listed antipsychotics may include coma.

~~Neuroleptics~~Antipsychotics		
Pimozide **Sertindole** **Quetiapine** No interaction study performed	Based on theoretical considerations, tipranavir, co-administered with low dose ritonavir, is expected to increase pimozide~~ and~~, sertindole and quetiapine concentrations. Inhibition of CYP 3A4 by tipranavir/r	The concomitant use of Aptivus, co-administered with low dose ritonavir, with pimozide, ~~or~~ sertindole, or quetiapine is contraindicated due to potential serious and/or life threatening events, including coma (see section 4.3)

PL

The wording implemented in the PL is that proposed by the PRAC and adopted by the CHMP.

- quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder)

In addition, the list of local representatives in the PL has been revised to add contact details for the representative of Croatia.

3. Overall conclusion and impact on the benefit/risk balance

Following assessment of a signal of an interaction between lopinavir/ritonavir and quetiapine by the PRAC, it was concluded that the MAHs of all other protease inhibitor-containing medicinal products (ATC code J05AE) should introduce a contraindication of use with quetiapine in the product information for these medicines. Indeed, the concomitant administration of HIV protease inhibitors is explicitly contra-indicated in the product information of quetiapine-containing medicinal products due to the risk of increased quetiapine exposure. In contrast, the same contraindication is not reported in the product information for the protease inhibitor-containing medicinal products (ATC code J05AE). In line with this request, the MAH for tipranavir submitted the present application. The SmPC changes proposed by the MAH were deemed acceptable to the CHMP since the content remains in line with the PRAC original conclusions. The wording implemented in the PL is that proposed by the PRAC and adopted by the CHMP.

The benefit / risk balance for this product remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	II

Update of sections 4.3 and 4.5 of the SmPC to include information regarding quetiapine following a class labelling for all HIV protease inhibitors. The PL was updated accordingly.

In addition, the MAH took the opportunity to add Croatia to the list of local representatives in the Package Leaflet.

Furthermore, minor linguistic changes (linguistic corrections) were introduced to the German/Austrian, Italian and Spanish product information.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.