



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 June 2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Telzir

fosamprenavir

Procedure No.: EMEA/H/C/000534/II/0058

Note

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



CHMP variation assessment report

Type II variation EMEA/H/C/000534/II/0058

Invented name/name:	Telzir
International non-proprietary name/common name:	fosamprenavir
Indication summary (as last approved):	treatment of HIV-1 infection
Marketing authorisation holder:	ViiV Healthcare UK Limited

1. Scientific discussion

1.1. Introduction

The active substance of Telzir, fosamprenavir (FPV), is a Protease Inhibitor (PI) of HIV. After oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. Amprenavir is a competitive inhibitor of the HIV-1 protease.

Telzir is available as 700 mg film-coated tablet and as 50 mg/mL oral suspension.

Telzir in combination with low dose ritonavir (RTV) is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, adolescents and children of 6 years and above in combination with other antiretroviral medicinal products. Telzir must only be given with low dose ritonavir as a pharmacokinetic enhancer of amprenavir and in combination with other antiretroviral medicinal products.

The recommended dose of Telzir in adults and adolescents (over 39 kg) is 700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily. The dose of Telzir in paediatric patients is based on body weight and is 18 mg/kg fosamprenavir twice daily with 3 mg/kg ritonavir twice daily, up to the adult dose.

The European Commission (EC) issued on 12 July 2004 a Marketing Authorisation for Telzir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults. An extension of indication in adolescents and children of 6 years and above was granted by the EC in September 2007.

On 10 December 2010, the MAH submitted a type II variation to include information related to drug interactions with Alfuzosin, an alpha-1 receptor antagonist, and phosphodiesterase type 5 (PDE5) inhibitors.

This variation has been classified as follow:

Variation(s) requested	Type
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data

1.2. Clinical aspects

Following oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium.

Amprenavir is primarily metabolised by the liver with less than 1% excreted unchanged in the urine. The primary route of metabolism is via the cytochrome P450 3A4 enzyme. Amprenavir metabolism is inhibited by ritonavir, via inhibition of CYP3A4, resulting in increased plasma concentrations of amprenavir. Amprenavir is also an inhibitor of CYP3A4; however it is less potent than ritonavir. In addition to exerting potent CYP3A4 inhibition, ritonavir inhibits CYP2D6 and induces CYP1A2, CYP2C9, and glucuronosyl transferase.

The current labelling of fosamprenavir states that drugs that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with fosamprenavir and ritonavir.

Interaction with Alfuzosin

Alfuzosin is an alpha-1 receptor antagonist used in the management of hypertension and benign prostatic hypertrophy. Alfuzosin is partially metabolised and excreted mainly in the bile and faeces. None of the metabolites found in man has any pharmacodynamic activity. CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin.

To date, no pharmacokinetic or clinical studies have examined the effect of alfuzosin when used together with fosamprenavir (with or without ritonavir).

However, there is a potential theoretical interaction with CYP3A4 inhibitors such as fosamprenavir. The likelihood of an interaction is further increased as fosamprenavir is coadministered with ritonavir.

Interaction with PDE5 inhibitors

PDE5 inhibitors (e.g. sildenafil, tadalafil) are used in the management of erectile dysfunction and more recently for pulmonary arterial hypertension. These indications have different dosages.

At doses of 50 mg (not to exceed 100 mg per day), sildenafil (Viagra) is indicated in the treatment of erectile dysfunction in men. Due to its ability to relax pulmonary vascular smooth muscle to increase exercise capacity, sildenafil (Revatio) is indicated in the treatment of pulmonary arterial hypertension (PAH) at a dose of 20 mg three times daily (TID)³.

PDE5 inhibitors metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4.

To date, no pharmacokinetic or clinical studies have examined the effect of PDE5 inhibitors when used together with fosamprenavir (with or without ritonavir).

The current labelling already contains information about avoiding coadministration due to increased levels of PDE5 inhibitors, but only refers to 'Erectile dysfunction agents'.

Discussion and changes to the product information

To reflect the potential drug interactions with alfuzosin and PDE5 inhibitors, the MAH proposed to update the table of interaction in section 4.5 to include alfuzosin and reword the mention of PDE5 inhibitors to cover use in both pulmonary arterial hypertension and erectile dysfunction indications. The MAH proposed to update section 2 of the package leaflet accordingly.

The co-administration of alfuzosin with CYP3A inhibitor as fosamprenavir and especially ritonavir which is always co-administered with fosamprenavir as a booster, could increase plasma concentration of alfuzosin and therefore be associated with serious adverse event. Therefore the MAH proposal of adding only a statement in section 4.5 of the SmPC and a warning in PL is not considered acceptable by the CHMP.

The CHMP recommends that co-administration of fosamprenavir /ritonavir with alfuzosin should be contraindicated as it is the case for other PIs.

With regards to interaction with PDE5 inhibitors, the CHMP is of the view that as for other boosted PIs, a difference should be made between PDE5 inhibitors when used for the treatment of pulmonary arterial hypertension (PAH) and when used for erectile dysfunction.

Available data on co-administration of ritonavir at steady state dose (500 mg BID) with sildenafil (100 mg single dose) resulted in a 4-fold and 11-fold increase in sildenafil C_{max} and AUC respectively^{1,2}. Given the pharmacokinetic interaction and resulting increased potential for sildenafil-associated adverse events (which include hypotension and syncope, etc.), and the inability to further downward adjust the sildenafil dose below 20 mg, co-administration of sildenafil (Revatio) with ritonavir is contraindicated in pulmonary arterial hypertension patients in the Revatio SmPC³.

Therefore, as Telzir is always co-administered with ritonavir as a booster, co-administration with sildenafil in PAH patients should be contraindicated.

As regards the use of PDE5 inhibitors in erectile dysfunction, the CHMP recommends that the warning should be in line with other boosted PIs with the same level of recommendation.

Consequently, the following changes have been made to the product information:

SmPC section 4.3, Contraindication

“Telzir must not be administered concurrently with medicinal products with narrow therapeutic windows that are substrates of cytochrome P450 3A4 (CYP3A4), e.g. alfuzosin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, pimozide, quinidine, terfenadine, oral midazolam (for caution on parenterally administered midazolam, see section 4.5), oral triazolam, sildenafil used for the treatment of pulmonary arterial hypertension (for use of sildenafil in patients with erectile dysfunction, see sections 4.4 and 4.5).”

SmPC section 4.4, Special warnings and precautions for use

“PDE5 inhibitors used for the treatment of erectile dysfunction: The use of Telzir concomitantly with PDE5 inhibitors (e.g. sildenafil ~~and~~, tadalafil, vardenafil) is not recommended (see section 4.5).

Co-administration of Telzir with low dose ritonavir and these medicinal products is expected to substantially increase their concentrations and may result in PDE5 inhibitor-associated adverse events such as hypotension, visual changes and priapism (see section 4.5). Note that co-administration of Telzir with low dose ritonavir with sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).”

SmPC section 4.5, Interaction with other medicinal products and other forms of interaction

ERECTILE DYSFUNCTION MEDICINAL PRODUCTS (PDE5 INHIBITORS)		
Sildenafil Vardenafil Tadalafil No drug interaction studies.	PDE5 inhibitors: ↑ expected (CYP3A4 inhibition by FPV/RTV)	Concomitant use is not recommended. It may result in an increase in PDE5 inhibitor-associated adverse reactions, including hypotension, visual changes and priapism (refer to PDE5 inhibitor prescribing information). Patients should be warned about these possible side effects when using PDE5 inhibitors with Telzir/ritonavir (see section 4.4). Note that co-administration of Telzir with low dose ritonavir with sildenafil used for the treatment of pulmonary arterial hypertension is contraindicated (see section 4.3).

ALPHA 1- ADRENORECEPTOR ANTAGONIST		
<u>Alfuzosin</u>	<u>Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by fosamprenavir/ritonavir.</u>	<u>Co-administration of TELZIR/ritonavir with alfuzosin is contraindicated (see section 4.3)</u>

Package Leaflet – section 2

“Don’t take Telzir:

...

- if you are taking any of these medicines
- alfuzosin (used to treat a prostate problem)

...

- sildenafil if used to treat pulmonary arterial hypertension, (a condition affecting the blood vessels to your lungs)

...

These medicines are not recommended with Telzir/ritonavir:

- sildenafil ~~and~~, vardenafil or tadalafil (used to treat erectile dysfunction) "

In addition, the MAH has updated the list of representatives in the package leaflet:

"Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
~~info@glaxosmithkline.dk~~ dk-info@gsk.com

Ísland
GlaxoSmithKline ehf.
Sími: + 354 530 3700

Slovenská republika
GlaxoSmithKline Slovakia s. r. o.
Tel: + 421 (0)2 ~~49 10 33~~ 48 26 11 11
repcia.sk@gsk.com

Κύπρος
GlaxoSmithKline (Cyprus) Ltd
Τηλ: + 357 22 ~~89 95 01~~ 39 70 00"

Annex II

Finally, Annex II has been updated according to the latest QRD recommendations:

"Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, ~~as described in version 7.2~~ presented in Module 1.8.1 of the Marketing Authorisation ~~Application~~ is in place and functioning before and whilst the product is on the market."

2. Conclusion

On 17 March 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted).

3. References

1. Gupta M, Kovar A, and Meibohm B. The Clinical Pharmacokinetics of Phosphodiesterase-5 Inhibitors for Erectile Dysfunction. J Clin Pharmacol 2005;45:987-1003.
2. Croom KF and Curran MP. Sildenafil: A Review of its Use in Pulmonary Arterial Hypertension. Drugs 2008; 68 (3): 383-397
3. Revatio (Sildenafil) Summary of Product Characteristics. March 2011.