14 July 2022
EMA/PRAC/139811/2022 Corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 7-10 March 2022 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

1. Alemtuzumab – Vitiligo (EPITT no 19737)

Summary of product characteristics

4.8. Undesirable effects

Skin and subcutaneous tissues disorders

Frequency uncommon: Vitiligo

Package leaflet

4. Possible side effects

These are the side effects that you may experience:

Uncommon (may affect up to 1 in 100 people)

- Patches of skin that have lost colour (vitiligo)

[1] Minor updates were implemented on 14 July 2022 for the Afinitor and Votubia product information as a paragraph from the March 2022 PRAC recommendation had been omitted in the initial document published on 4 April 2022 (see pages 4 and 5).

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2. Calcineurin inhibitors for systemic use (ciclosporin; tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors for systemic use (everolimus; sirolimus; temsirolimus) – Drug interaction with cannabidiol leading to calcineurin inhibitors and mTOR inhibitors serum levels increased and toxicity (EPITT no 19614)

Tacrolimus

Summary of product characteristics

- 4.4. Special warnings and precautions for use

CYP3A4 inhibitors
[…]

CYP3A4 inducers
[…]

P-glycoprotein

Caution should be observed when co-administering tacrolimus with drugs that inhibit P-glycoprotein, as an increase in tacrolimus levels may occur. Tacrolimus whole blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the tacrolimus dose may be required (see section 4.5).

- 4.5. Interaction with other medicinal products and other forms of interaction

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
[…]	[…]	[…]
Cannabidiol (P-gp inhibitor)	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to increased bioavailability of tacrolimus.	Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus dose if needed (*see sections 4.2 and 4.4*).

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

[…]

In particular, you should tell your doctor if you are taking or have recently taken medicines with active substances like:

[…]

- Cannabidiol (uses amongst others include treatment of seizures)

Ciclosporin

Summary of product characteristics

- 4.4. Special warnings and precautions for use

Interactions

Caution should be observed when co-administering ciclosporin with drugs that substantially increase or decrease ciclosporin plasma concentrations, through inhibition or induction of CYP3A4 and/or Pglycoprotein (see section 4.5).

Renal toxicity should be monitored when initiating ciclosporin use together with active substances that increase ciclosporin levels or with substances that exhibit nephrotoxic synergy (see section 4.5). The clinical condition of the patient should be monitored closely. Monitoring of ciclosporin blood levels and adjustment of the ciclosporin dose may be required.

[…]

- 4.5. Interaction with other medicinal products and other forms of interaction

Drug interactions

[…]

Drugs that increase ciclosporin levels

All inhibitors of CYP3A4 and/or P-glycoprotein may lead to increased levels of ciclosporin.

[…]

Cannabidiol (P-gp inhibitor): There have been reports of increased blood levels of another calcineurin inhibitor during concomitant use with cannabidiol. This interaction may occur due to inhibition of intestinal P-glycoprotein efflux, leading to increased bioavailability of the calcineurin inhibitor. Ciclosporin and cannabidiol should therefore be co-administered with caution, closely monitoring for side effects. In transplant recipients, monitor ciclosporin whole blood trough concentrations and adjust the ciclosporin dose if needed. In non-transplant patients, monitoring of ciclosporin blood levels, with dose adjustment if needed, should be considered (see sections 4.2 and 4.4).

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular tell your doctor or pharmacist if you are taking any of the following medicines before or during [product name] treatment:

[…]

- Medicines which may increase or decrease the level of ciclosporin (the active substance of [product name]) in your blood. Your doctor might check the level of ciclosporin in your blood when starting or stopping treatment with other medicines.
    - Medicines which may increase the level of ciclosporin in your blood include: […] Cannabidiol (uses amongst others include treatment of seizures).

Everolimus (Afinitor)

Summary of product characteristics

- 4.4. Special warnings and precautions for use

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, the clinical condition of the patient should be monitored closely. Dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5).

Concomitant treatment with potent CYP3A4/PgP inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and potent inhibitors is not recommended.[2]

[…]

- 4.5. Interaction with other medicinal products and other forms of interaction

[…]

Table 2 Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/Cmax Geometric mean ratio (observed range)	Recommendations concerning co-administration
[…]		
Moderate CYP3A4/PgP inhibitors		
[…]	[…]	[…]
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) Cmax ↑1.8-fold (range 1.3-2.6)	Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended (see sections 4.2 and 4.4). […]
Cannabidiol (P-gp inhibitor)	AUC ↑ 2.5-fold Cmax ↑ 2.5-fold	

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

[Product name] may affect the way some other medicines work. If you are taking other medicines at the same time as [product name], your doctor may need to change the dose of [product name] or the

[2] This paragraph from the PRAC recommendation on Afinitor had been omitted in the initial document published on 4 April 2022 and has been added through the correction of 14 July 2022.

other medicines. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following may increase the risk of side effects with [product name]:

[…]

- Cannabidiol (uses amongst others include treatment of seizures).

Everolimus (Votubia)

Summary of product characteristics

- 4.4. Special warnings and precautions for use

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, the clinical condition of the patient should be monitored closely. Monitoring of everolimus trough concentrations and dose adjustments of Votubia may be required (see section 4.5).

Concomitant treatment with potent CYP3A4/Pgp inhibitors result in dramatically increased blood concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Votubia and potent inhibitors is not recommended.[3]

[…]

- 4.5. Interaction with other medicinal products and other forms of interaction

[…]

CYP3A4 and PgP inhibitors increasing everolimus concentrations

[…]

Table 2 Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/Cmax Geometric mean ratio (observed range)	Recommendations concerning co-administration
[…]		
Moderate CYP3A4/PgP inhibitors		
[…]	[…]	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. […]
Ciclosporin oral	[…]	
Cannabidiol (P-gp inhibitor)	AUC ↑ 2.5-fold Cmax ↑ 2.5-fold	

[3] This paragraph from the PRAC recommendation on Votubia had been omitted in the initial document published on 4 April 2022 and has been added through the correction of 14 July 2022.

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

[Product name] may affect the way some other medicines work. If you are taking other medicines at the same time as [product name], your doctor may need to change the dose of [product name] or the other medicines. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following may increase the risk of side effects with [product name]:

- Cannabidiol (uses amongst others include treatment of seizures).

Everolimus (Certican)

Summary of product characteristics

- 4.4. Special warnings and precautions for use

Interaction with strong inhibitors or inducers of CYP3A4 and/or P-glycoprotein (PgP)

Co-administration with strong inhibitors of CYP3A4 ~~inhibitors~~ and/or the multidrug efflux pump P-glycoprotein (PgP) (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) may increase everolimus blood levels and is not recommended unless the benefit outweighs the risk.

Coadministration with ~~and~~ strong inducers of CYP3A4 and/or PgP (e.g. rifampicin, rifabutin, carbamazepine, phenytoin) is not recommended unless the benefit outweighs the risk.

If coadministration of inducers or inhibitors of CYP3A4 and/or PgP cannot be avoided, i~~I~~t is recommended that everolimus whole blood trough concentrations and the clinical condition of the patient be monitored while they ~~whenever inducers or inhibitors of CYP3A4~~ are concurrently administered with everolimus and after their discontinuation. Dose adjustments of everolimus may be required (see section 4.5).

- 4.5. Interaction with other medicinal products and other forms of interaction

[…]

Table 3 Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/Cmax Geometric mean ratio (observed range)	Recommendations concerning co-administration
[…]		
Moderate CYP3A4/PgP inhibitors		
[…]	[…]	

Ciclosporin oral	[…]	Everolimus whole blood trough concentrations should be monitored whenever inhibitors of CYP3A4/PgP are concurrently administered and after their discontinuation. […] Closely monitor for side effects and adjust the everolimus dose as needed (see sections 4.2 and 4.4).
Cannabidiol (P-gp inhibitor)	AUC ↑ 2.5-fold Cmax ↑ 2.5-fold	

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. Certain medicines may affect the way in which [product name] works in the body. It is very important that you tell your doctor if you are taking any of the following medicines:

[…]

- Cannabidiol (uses amongst others include treatment of seizures).

Temsirolimus

Summary of product characteristics

- 4.4. Special warnings and precautions for use

Agents inhibiting CYP3A metabolism

[…]

Agents affecting P-glycoprotein

Concomitant use of mTOR inhibitors with inhibitors of P-glycoprotein (P-gp) may increase mTOR inhibitor blood levels. Caution should be observed when co-administering temsirolimus with drugs that inhibit P-glycoprotein. The clinical condition of the patient should be monitored closely. Dose adjustments of temsirolimus may be required (see section 4.5).

Vaccinations

[…]

- 4.5. Interaction with other medicinal products and other forms of interaction

Agents inhibiting CYP3A metabolism

[…]

Concomitant treatment with moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, clarithromycin, erythromycin, aprepitant, amiodarone) should only be administered with caution in patients receiving 25 mg and should be avoided in patients receiving temsirolimus doses higher than 25 mg.

Cannabidiol (P-gp inhibitor)

There have been reports of increased blood levels of other mTOR inhibitors during concomitant use with cannabidiol. Coadministration of cannabidiol with another orally administered mTOR inhibitor in a healthy volunteer study lead to an increase in exposure to the mTOR inhibitor of approximately 2.5-fold for both Cmax and AUC, due to inhibition of intestinal P-gp efflux by cannabidiol. Temsirolimus was demonstrated to be a substrate for P-gp in vitro. Cannabidiol should be co-administered with temsirolimus with caution, closely monitoring for side effects and adjusting the temsirolimus dose as needed (see sections 4.2 and 4.4).

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. Some medicines can interfere with the breakdown or metabolism of [product name] and therefore dose adjustment of [product name] may be required. In particular, you should inform your doctor or pharmacist if you are taking any of the following:

[…]

- Cannabidiol (uses amongst others include treatment of seizures).

Sirolimus

Summary of product characteristics

- 4.4. Special warnings and precautions for use

Concomitant therapy

Cytochrome P450 isozymes and P-glycoprotein

Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (P-gp) (such as ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) may increase sirolimus blood levels and is not recommended. ~~or~~

Coadministration with strong inducers of CYP3A4 and/or P-gp (such as rifampin, rifabutin) is not recommended.

If coadministration of inducers or inhibitors of CYP3A4 and/or P-gp cannot be avoided, it is recommended that sirolimus whole blood trough concentrations and the clinical condition of the patient be monitored while they are concurrently administered with sirolimus and after their discontinuation. Dose adjustments of sirolimus may be required (see section 4.5).

- 4.5. Interaction with other medicinal products and other forms of interaction

[…]

Ciclosporin (CYP3A4 substrate)

[…]

Cannabidiol (P-gp inhibitor)

There have been reports of increased blood levels of sirolimus during concomitant use with cannabidiol. Coadministration of cannabidiol with another orally administered mTOR inhibitor in a healthy volunteer study lead to an increase in exposure to the mTOR inhibitor of approximately 2.5-fold for both Cmax and AUC, due to inhibition of intestinal P-gp efflux by cannabidiol. Cannabidiol should be co-administered with sirolimus with caution, closely monitoring for side effects. Monitor sirolimus blood levels and adjust the dose as needed (see sections 4.2 and 4.4).

Package leaflet

- 2. What you need to know before you take [product name]

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines can interfere with the action of [product name] and, therefore, dose adjustment of [product name] may be required. In particular, you should inform your doctor or pharmacist if you are taking any of the following:

[…]

- Cannabidiol (uses amongst others include treatment of seizures).

3. Elasomeran (COVID-19 mRNA vaccine - Spikevax) – Capillary leak syndrome (EPITT no 19743)

Summary of product characteristics

4.4. Special warnings and precautions for use

Capillary leak syndrome flare-ups

A few cases of capillary leak syndrome (CLS) flare-ups have been reported in the first days after vaccination with Spikevax. Healthcare professionals should be aware of signs and symptoms of CLS to promptly recognise and treat the condition. In individuals with a medical history of CLS, planning of vaccination should be made in collaboration with appropriate medical experts.

Package leaflet

2. Warnings and precautions

Capillary leak syndrome (CLS) flare-ups

A few cases of capillary leak syndrome flare-ups (causing fluid leakage from small blood vessels (capillaries) resulting in rapid swelling of the arms and legs, sudden weight gain and feeling faint, low blood pressure) have been reported following vaccination with Spikevax. If you have previously had episodes of CLS, talk to a doctor before you are given Spikevax.