



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

### Adopted at the 7-10 March 2022 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 7-10 March 2022 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>2</sup> reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines web portal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (21-24 March 2022) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available [guidance](#). Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

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<sup>1</sup> Expected publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

<sup>2</sup> The relevant EPITT reference number should be used in any communication related to a signal.



The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the [Questions and Answers on signal management](#).

# 1. Recommendations for update of the product information<sup>3</sup>

## 1.1. Alemtuzumab – Vitiligo

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19737
<b>PRAC Rapporteur</b>	Anette Kirstine Stark (DK)
<b>Date of adoption</b>	10 March 2022

### Recommendation

Having considered the available evidence ascertained from EudraVigilance, the scientific literature, nonclinical and clinical data and additional data submitted by the MAH, the PRAC has agreed that the MAH for Lemtrada (Sanofi Belgium) should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

#### Summary of product characteristics

4.8. Undesirable effects

SOC: 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)

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<sup>3</sup> Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the [EMA website](#).

**1.2. 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**

<b>Authorisation procedure</b>	Centralised and non-centralised
<b>EPITT No</b>	19614
<b>PRAC Rapporteur</b>	Ronan Grimes (IE)
<b>Date of adoption</b>	10 March 2022

## Recommendation

The PRAC has considered the responses from Astellas, Novartis and Pfizer and the available data from EudraVigilance and the literature regarding the risk of interaction of cannabidiol with calcineurin inhibitors (tacrolimus, ciclosporin) or mTOR inhibitors (everolimus, sirolimus, temsirolimus). The PRAC has also considered the results of a recent drug-drug interaction study between cannabidiol and everolimus (procedure EMEA/H/C/004675/II/0015) which demonstrated that exposure to everolimus was increased by 2.5-fold for C<sub>max</sub> and AUC when it was co-administered with cannabidiol. The PRAC agrees that there is sufficient evidence to recommend the inclusion of information regarding the risk of interaction with cannabidiol in the product information of calcineurin inhibitors and mTOR inhibitors.

The MAHs of medicinal products for systemic use containing tacrolimus, ciclosporin, everolimus, sirolimus or temsirolimus should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information of their respective products as described below (<new text underlined>/<text to be removed with ~~strikethrough~~>).

## Tacrolimus

### Summary of product characteristics

- 4.4. Special warnings and precautions for use

#### *CYP3A4 inhibitors*

Concomitant use with CYP3A4 inhibitors may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity, neurotoxicity and QT prolongation. [...]

#### *CYP3A4 inducers*

Concomitant use with CYP3A4 inducers may decrease tacrolimus blood levels, potentially increasing the risk of transplant rejection. [...]

#### *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
[...]	[...]	[...]
<u>Cannabidiol (P-gp inhibitor)</u>	<u>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.</u>	<u>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).</u>

### 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.

[...]

Concomitant use of ciclosporin and tacrolimus should be avoided.

Ciclosporin is an inhibitor of CYP3A4, [...]

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

#### Drug interactions

[...]

Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular CYP3A4.

[...]

Medicinal products known to reduce or increase the bioavailability of ciclosporin: In transplant patients frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of the co-administered medication. In nontransplant patients the relationship between blood level and clinical effects is less well established. If medicinal products known to increase ciclosporin levels are given concomitantly, frequent assessment of renal function and careful monitoring for ciclosporin-related side effects may be more appropriate than blood level measurement.

[...]

#### 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.

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

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 2 below.

#### CYP3A4 and PgP inhibitors increasing everolimus concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

[...]

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
<i>Potent CYP3A4/PgP inhibitors</i>		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) Cmax ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Afinitor and potent inhibitors is not recommended.
[...]	Not studied. Large increase in everolimus concentration is expected.	
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
<i>Moderate CYP3A4/PgP inhibitors</i>		
[...]	[...]	

Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) Cmax ↑1.8-fold (range 1.3-2.6)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended ( <u>see sections 4.2 and 4.4</u> ). If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration.
<u>Cannabidiol (P-gp inhibitor)</u>	<u>AUC ↑ 2.5-fold</u> <u>Cmax ↑ 2.5-fold</u>	

### 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 (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.

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

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 2 below.

#### CYP3A4 and PgP inhibitors increasing everolimus concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

[...]

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
<i>Potent CYP3A4/PgP inhibitors</i>		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) Cmax ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Votubia and potent inhibitors is not recommended.
[...]	Not studied. Large increase in everolimus concentration is expected.	
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
<i>Moderate CYP3A4/PgP inhibitors</i>		
[...]	[...]	

Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) Cmax ↑1.8-fold (range 1.3-2.6)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided.
<u>Cannabidiol (P-gp inhibitor)</u>	<u>AUC ↑ 2.5-fold</u> <u>Cmax ↑ 2.5-fold</u>	<p><i>For patients with renal angiomyolipoma associated with TSC:</i> If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Votubia dose is returned to the dose used prior to initiation of the co-administration (see also Therapeutic drug monitoring in section 4.2).</p> <p><i>For patients with SEGA associated with TSC:</i> If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the daily dose by approximately 50%. Further dose reduction may be required to manage adverse reactions (see sections 4.2 and 4.4). Everolimus trough concentrations should be assessed at least 1 week after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination</p>

		time for most commonly used moderate inhibitors) before the Votubia dose is returned to the dose used prior to initiation of the co-administration. The everolimus trough concentration should be assessed at least 1 week later (see sections 4.2 and 4.4).
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**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, it 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

Everolimus is mainly metabolised by CYP3A4 in the liver and to some extent in the intestinal wall and is a substrate for the multidrug efflux pump, P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by medicinal products that affect CYP3A4 and/or P-glycoprotein. Concurrent treatment with strong 3A4 inhibitors and

inducers is not recommended. Inhibitors of P-glycoprotein may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentrations. In vitro, everolimus was a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. All in vivo interaction studies were conducted without concomitant ciclosporin.

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
<i>Strong CYP3A4/PgP inhibitors</i>		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) Cmax ↑4.1-fold (range 2.6-7.0)	Co-administration with strong CYP3A4/PgP-inhibitors is not recommended unless the benefit outweighs the risk
[...]	Not studied. Large increase in everolimus concentration is expected.	
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
<i>Moderate CYP3A4/PgP inhibitors</i>		
[...]	[...]	Everolimus whole blood trough concentrations should be monitored whenever inhibitors of CYP3A4/PgP are concurrently administered and after their discontinuation. Use caution when coadministration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. <u>Closely monitor for side effects and adjust the everolimus dose as needed (see sections 4.2 and 4.4).</u>
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) Cmax ↑1.8-fold (range 1.3-2.6)	
<u>Cannabidiol (P-gp inhibitor)</u>	<u>AUC ↑ 2.5-fold</u> <u>Cmax ↑ 2.5-fold</u>	

### 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

Co-administration of temsirolimus 5 mg with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus C<sub>max</sub> or AUC; however, sirolimus AUC increased 3.1-fold, and AUC<sub>sum</sub> (temsirolimus + sirolimus) increased 2.3-fold compared to temsirolimus alone. The effect on the unbound concentrations of sirolimus has not been determined, but is expected to be larger than the effect on whole-blood concentrations due to the saturable binding to red blood cells. The effect may also be more pronounced at a 25 mg dose. Therefore, substances that are potent inhibitors of CYP3A4 activity (e.g. nelfinavir, ritonavir, itraconazole, ketoconazole, voriconazole, nefazodone) increase sirolimus blood concentrations. Concomitant treatment of temsirolimus with these agents should be avoided (see section 4.4).

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 C<sub>max</sub> 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

Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp) located in the small intestine. Therefore, absorption and the subsequent elimination of sirolimus may be influenced by substances that affect these proteins. Inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) decrease the metabolism of sirolimus and increase sirolimus levels. Inducers of CYP3A4 (such as rifampin or rifabutin) increase the metabolism of sirolimus and decrease sirolimus levels. Co-administration of sirolimus with strong inhibitors of CYP3A4 or inducers of CYP3A4 is not recommended (see section 4.4).

[...]

#### 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 C<sub>max</sub> 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).

### **1.3. Elasomeran (COVID-19 mRNA vaccine - Spikevax) – Capillary leak syndrome**

<b>Authorisation procedure</b>	Centralised
<b>EPITT No</b>	19743
<b>PRAC Rapporteur</b>	Marie Louise Schougaard Christiansen (DK)
<b>Date of adoption</b>	10 March 2022

## Recommendation

Having considered the available evidence from the cumulative review submitted by the Marketing Authorisation Holder (MAH) of the COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.), the PRAC concluded that a few cases of capillary leak syndrome (CLS) flare-ups reported with Spikevax merit a warning in the product information. The PRAC agreed that the MAH of Spikevax should submit a variation by 8 April 2022, to amend the product information as described below (new text underlined):

### **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.

## 2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Pneumococcal polysaccharide vaccine (23 serotypes)	Extensive swelling of vaccinated limb (19768)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 4 May 2022)	MSD Sharp & Dohme GmbH
Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline; and Serotonin-norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine; duloxetine; milnacipran; venlafaxine; and Mirtazapine; vortioxetine	Pulmonary hypertension (19772)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 4 May 2022)	Pfizer, GSK, Eli Lilly, Mylan, H. Lundbeck, Almirall, Pierre Fabre, N.V. Organon
Tocilizumab	Pancreatitis (19777)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 9 July 2022)	Roche Registration GmbH

## 3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Sacubitril, valsartan	Vasoplegia syndrome (19739)	Anette Kirstine Stark (DK)	Routine pharmacovigilance	Novartis Europharm Limited
Tozinameran (COVID-19 mRNA vaccine - Comirnaty)	Capillary leak syndrome (19743)	Menno van der Elst (NL)	Routine pharmacovigilance	BioNTech Manufacturing GmbH