6 January 2022[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 29 November-2 December 2021 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 29 November-2 December 2021 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] 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 webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (13-16 December 2021) 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.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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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.

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

1.1. Olmesartan; olmesartan, amlodipine; olmesartan, hydrochlorothiazide; olmesartan medoxomil, amlodipine besilate, hydrochlorothiazide – Autoimmune hepatitis[3]

Authorisation procedure	Non-centralised
EPITT No	19258
PRAC rapporteur	Martin Huber (DE)
Date of adoption	2 December 2021

Recommendation

Taking into consideration the available evidence from the published literature and EudraVigilance, the PRAC has concluded that a causal association between autoimmune hepatitis and patients treated with olmesartan-containing products is of a reasonable possibility.

PRAC has agreed that the MAHs of olmesartan-containing medicinal products (including fixed-dose combinations) should therefore submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information to include autoimmune hepatitis and additionally, to delete a definite enumeration in the heading in the PIL as described below (new text underlined, text to be removed ~~strikethrough~~).

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions (for fixed-dose combinations in the column relating to olmesartan mono-substance):

SOC Hepatobiliary disorders

Frequency not known: Autoimmune hepatitis*

Case description below the tabulated summary of adverse reactions:

*Cases of autoimmune hepatitis with a latency of few months to years have been reported post-marketing, that were reversible after the withdrawal of olmesartan.

Package leaflet

4. Possible side effects

Section below the heading dealing with serious side effects requiring immediate action/medical attention:

[...] the following ~~two~~ side effects can be serious:
[...]

Frequency not known: If you experience yellowing of the whites of the eyes, dark urine, itching of the skin, even if you started therapy with X longer time ago, **contact your doctor immediately** who will evaluate your symptoms and decide on how to continue your blood pressure medication.

[3] 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. COVID-19 mRNA[4] vaccine (nucleoside-modified) – Spikevax – Myocarditis and pericarditis[5]

Authorisation procedure	Centralised
EPITT No	19713
PRAC rapporteur	Hans Christian Siersted (DK)
Date of adoption	2 December 2021

Recommendation

Having considered the available evidence from large observational studies in and outside the EEA, as well as the data provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should submit by Monday 6 December (by 9am CET time) a variation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Myocarditis and pericarditis

There is an increased risk for ~~Very rare cases of~~ myocarditis and pericarditis ~~have been observed~~ following vaccination with Spikevax.

These ~~cases~~ conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days ~~following vaccination~~. They have been observed more often after the second vaccination, and more often in younger ~~men~~ males (see section 4.8).

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

4.8. Undesirable effects

SOC cardiac disorders:

[Frequency] ~~not known~~ Very rare: Myocarditis

[Frequency] ~~not known~~ Very rare: Pericarditis

[4] Messenger ribonucleic acid
[5] Translations in all EU languages have already been included in the Spikevax product information.

Description of selected adverse reactions

Myocarditis

The increased risk of myocarditis after vaccination with Spikevax is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Spikevax. One study showed that in a period of 7 days after the second dose there were about 1.316 (95% CI 1.299 – 1.333) extra cases of myocarditis in 12-29 year old males per 10,000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 1.88 (95% CI 0.956 – 2.804) extra cases of myocarditis in 16-24 year old males per 10,000 compared to unexposed persons.

Package leaflet

2. What you need to know before you receive Spikevax

Warning and precautions

There is an increased risk ~~Very rare cases~~ of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) ~~have been reported~~ after vaccination with Spikevax (see section 4).

These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. ~~The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men.~~

Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

4. Possible side effects

Frequency ~~"unknown"~~ Very rare (may affect up to 1 in 10,000 people): Inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

1.3. Tozinameran (previously COVID-19 mRNA[6] vaccine [nucleoside modified]) – Comirnaty – Myocarditis and pericarditis[7]

Authorisation procedure	Centralised
EPITT No	19712
PRAC rapporteur	Menno van der Elst (NL)
Date of adoption	2 December 2021

Recommendation

Having considered the available evidence from large observational studies in and outside the EEA, as well as the data provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty (BioNTech Manufacturing GmbH) should submit by Monday 6 December (by 9am CET time) a variation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Myocarditis and pericarditis

There is an increased risk ~~Very rare cases~~ of myocarditis and pericarditis ~~have been observed~~ following vaccination with Comirnaty. These ~~cases~~ conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days ~~following vaccination~~. They have been observed more often after the second vaccination, and more often in younger ~~men~~ males (see section 4.8). Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

4.8. Undesirable effects

SOC cardiac disorders:

[Frequency] ~~Not known~~ Very rare: Myocarditis[d], Pericarditis[d]

Description of selected adverse reactions

Myocarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

[6] Messenger ribonucleic acid
[7] Translations in all EU languages have already been included in the Comirnaty product information.

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10,000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.57 [95% CI 0.39 – 0.75] extra cases of myocarditis in 16-24 year old males per 10,000 compared to unexposed persons.

Package leaflet

2. What you need to know before you receive Comirnaty

Warning and precautions

There is an increased risk ~~Very rare cases~~ of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) ~~have been reported~~ after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often ~~occurred~~ in younger ~~men~~ males. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

4. Possible side effects

~~Not known (cannot be estimated from the available data)~~ Very rare side effects: may affect up to 1 in 10,000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Abatacept	Acute respiratory distress syndrome (ARDS) (19751)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 2 February 2022)	Bristol-Myers Squibb Pharma EEIG
Atezolizumab	Optic neuritis (19747)	Márcia Silva (PT)	Supplementary information requested (submission by 2 February 2022)	Roche Registration GmbH
COVID-19 mRNA[8] vaccine (nucleoside-modified) – Spikevax	Autoimmune hepatitis (19750)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 2 February 2022)	Moderna Biotech Spain, S.L.
Dabigatran	Autoimmune haemolytic anaemia (19745)	Anette Kirstine Stark (DK)	Assess in the next PSUR (submission by 27 May 2022)	Boehringer Ingelheim International GmbH
Liraglutide	Cutaneous amyloidosis (19740)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 30 March 2024)	Novo Nordisk A/S
Tozinameran (previously COVID-19 mRNA[8] vaccine [nucleoside modified]) – Comirnaty	Autoimmune hepatitis (19749)	Menno van der Elst (NL)	Supplementary information requested (submission by 2 February 2022)	BioNTech Manufacturing GmbH
Vildagliptin; vildagliptin, metformin	Cutaneous vasculitis (19742)	Annika Folin (SE)	Supplementary information requested (submission by 2 February 2022)	Novartis Europharm Limited

[8] Messenger ribonucleic acid

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Canakinumab	Interstitial lung disease (ILD) and alveolar proteinosis (19736)	Brigitte Keller-Stanislawski (DE)	No action (signal to be assessed in the ongoing PSUR procedure)	Novartis Europharm Limited