



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 9-12 January 2023 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 9-12 January 2023 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]³ 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 (23-26 January 2023) 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 EPITT reference numbers of 2 signals (Vaxzevria and myositis, Comirnaty and myositis) were corrected on 23 June 2023 (see page 9).

³ The relevant EPITT reference number should be used in any communication related to a signal.



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 information⁴

1.1. 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; rosuvastatin; simvastatin and other relevant fixed dose combinations; pravastatin, fenofibrate; simvastatin, fenofibrate – Myasthenia gravis

Authorisation procedure	Centralised and non-centralised
EPITT No	19822
PRAC Rapporteur	Nathalie Gault (FR)
Date of adoption	12 January 2023

Recommendation

Having reviewed the available evidence, including EudraVigilance and the scientific literature, the PRAC has concluded that the Marketing Authorisation Holders (MAHs) of atorvastatin, pravastatin, lovastatin, fluvastatin, simvastatin, rosuvastatin and pitavastatin containing products, both single-ingredient and fixed-dose combination products, 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

4.4. Special warnings and precautions for use

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). [Product name] should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

4.8. Undesirable effects

Nervous system disorders

Frequency not known: Myasthenia gravis

Eye disorders

Frequency not known: Ocular myasthenia

Package leaflet

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

Warning and precautions

Talk to your doctor or pharmacist before taking [product name]

If you have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used when breathing), or ocular myasthenia (a disease causing eye muscle weakness) as

⁴ Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the [EMA website](#).

statins may sometimes aggravate the condition or lead to the occurrence of myasthenia (see section 4).

4. Possible side effects

Adverse reactions with frequency not known:

Myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing).

Ocular myasthenia (a disease causing eye muscle weakness).

Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath.

1.2. Dabrafenib; trametinib – Haemophagocytic lymphohistiocytosis

Authorisation procedure	Centralised
EPITT No	19824
PRAC Rapporteur	Ulla Wändel Liminga
Date of adoption	12 January 2023

Recommendation

Having considered the available evidence and following the assessment of the data submitted by the concerned Marketing Authorisation Holder (MAH), the PRAC has agreed that the product information for dabrafenib and trametinib should be updated to reflect the risk of haemophagocytic lymphohistiocytosis (HLH) when the products are used in combination. Nevertheless, the PRAC did not support to explicitly state that discontinuation should be permanent, even in case of HLH being diagnosed.

If more evidence becomes available in the future, the MAH should consider whether further updates of the product information regarding HLH are necessary when the respective products are used in monotherapy.

Regarding frequency, given 3 cases among 3,373 subjects exposed in the registrational studies, a frequency of *rare* is considered justified.

In order to include HLH as an adverse reaction related to the combination dabrafenib trametinib in section 4.8, different changes in the table headers, footers and superscripts will be necessary as specified below.

The MAH of Tafinlar and Mekinist (Novartis Europharm Limited), should submit a variation within two months from the publication of the PRAC recommendation, to amend the product's information as described here (new text underlined and text to be removed ~~strike through~~):

Tafinlar (dabrafenib) - Summary of product characteristics

4.4. Special warnings and precautions for use

Haemophagocytic lymphohistiocytosis

In post-marketing experience, haemophagocytic lymphohistiocytosis (HLH) has been observed in patients treated with dabrafenib in combination with trametinib. Caution should be taken when

dabrafenib is administered in combination with trametinib. If HLH is confirmed, administration of dabrafenib and trametinib should be discontinued and treatment for HLH initiated.

4.8. Undesirable effects

Tabulated list of adverse reactions

Adverse reactions associated with dabrafenib obtained from clinical studies and post-marketing surveillance are tabulated below for dabrafenib monotherapy (Table 3) and dabrafenib in combination with trametinib (Table 4).

Adverse drug reactions are listed below [...]

Table 3 - Adverse reactions ~~reported in the integrated safety population of~~ with dabrafenib monotherapy ~~in the studies BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680 (n=578)~~

Table 4 - Adverse reactions ~~reported in the integrated safety population of~~ with dabrafenib in combination with trametinib ~~in the studies MEK115306, MEK116513^a, BRF113928, and BRF115532 (n=1076)~~

System organ class	Frequency (all grades)	Adverse reactions
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma ^{ab} Papilloma ^{bc}
	Uncommon	New primary melanoma ^{cd}
Immune system disorders	Uncommon	Hypersensitivity ^{de}
	Rare	Haemophagocytic lymphohistiocytosis
Vascular disorders	Very common	Haemorrhage ^{ef}
Gastrointestinal disorders	Very common	Abdominal pain ^{fg}
Skin and subcutaneous disorders	Very common	Erythema ^{gh}
Musculoskeletal and connective tissue disorders	Very common	Muscle spasms ^{hi}

^aThe safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease (uncommon). 3) The following adverse reaction has occurred in MEK116513 and BRF115532 but not in MEK115306 and BRF113928: rhabdomyolysis (uncommon)

^{ab} Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma

^{bc} Papilloma, skin papilloma

^{cd} Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III

^{de} Includes drug hypersensitivity

^{ef} Bleeding from various sites, including intracranial bleeding and fatal bleeding

^{fg} Abdominal pain upper and abdominal pain lower

^{gh} Erythema, generalised erythema

^{hi} Muscle spasms, musculoskeletal stiffness

Tafinlar (dabrafenib) - Package leaflet

2. What you need to know before you take Tafinlar

Conditions you may need to look out for

Immune system disorders

Tafinlar in combination with trametinib may in rare instances cause a condition (haemophagocytic lymphohistiocytosis or HLH) in which the immune system makes too many infection-fighting cells, called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems. Tell your doctor immediately if you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time.

4. Possible side effects

Possible serious side effects

Immune system disorders

If you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time, tell your doctor immediately. It may be a sign of a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis), see section 2 (frequency rare).

Mekinist (trametinib) - Summary of product characteristics

4.4. Special warnings and precautions for use

Haemophagocytic lymphohistiocytosis

In post-marketing experience, haemophagocytic lymphohistiocytosis (HLH) has been observed in patients treated with trametinib in combination with dabrafenib. Caution should be taken when trametinib is administered in combination with dabrafenib. If HLH is confirmed, administration of trametinib and dabrafenib should be discontinued and treatment for HLH initiated.

4.8. Undesirable effects

Tabulated list of adverse reactions

Adverse reactions associated with trametinib obtained from clinical studies and post-marketing surveillance are tabulated below for trametinib monotherapy (Table 4) and trametinib in combination with dabrafenib (Table 5).

Table 4 - Adverse reactions reported in the integrated safety population of with trametinib monotherapy (n=329)

Table 5 - Adverse reactions reported in the integrated safety population of with trametinib in combination with dabrafenib in the studies MEK115306, MEK116513^a, BRF113928, and BRF115532 (n=1,076)

System organ class	Frequency (all grades)	Adverse reactions
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma ^{ab} Papilloma ^{be}
	Uncommon	New primary melanoma ^{cd}
	Uncommon	Hypersensitivity ^{de}
Immune system disorders	Rare	<u>Haemophagocytic lymphohistiocytosis</u>

Vascular disorders	Very common	Haemorrhage ^{ef}
Gastrointestinal disorders	Very common	Abdominal pain ^{fg}
Skin and subcutaneous disorders	Very common	Erythema ^{gh}
Musculoskeletal and connective tissue disorders	Very common	Muscle spasms ^{hi}

^aThe safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease (uncommon). 3) The following adverse reaction has occurred in MEK116513 and BRF115532 but not in MEK115306 and BRF113928: rhabdomyolysis (uncommon)

^{ab} Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma

^{bc} Papilloma, skin papilloma

^{cd} Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III

^{de} Includes drug hypersensitivity

^{ef} Bleeding from various sites, including intracranial bleeding and fatal bleeding

^{fg} Abdominal pain upper and abdominal pain lower

^{gh} Erythema, generalised erythema

^{hi} Muscle spasms, musculoskeletal stiffness

Mekinist (trametinib) - Package leaflet

2. What you need to know before you take Mekinist

Conditions you need to look out for

Immune system disorders

Mekinist in combination with dabrafenib may in rare instances cause a condition (haemophagocytic lymphohistiocytosis or HLH) in which the immune system makes too many infection-fighting cells, called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems. Tell your doctor immediately if you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time.

4. Possible side effects

Possible serious side effects

Immune system disorders

If you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time, tell your doctor immediately. It may be a sign of a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis), see section 2 (frequency rare).

1.3. Regorafenib – Thrombotic microangiopathy

Authorisation procedure	Centralised
EPITT No	19832
PRAC Rapporteur	Menno van der Elst (NL)
Date of adoption	12 January 2023

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the plausibility of the interference on the Vascular Endothelial Growth Factor (VEGF) signalling pathway in the development of thrombotic microangiopathy, and the already known association of thrombotic angiopathy with other drugs targeting the VEGF pathway, PRAC has agreed that the Marketing Authorisation Holder (MAH) for Stivarga, (Bayer AG) 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

4.4. Special warnings and precautions for use

Thrombotic microangiopathy (TMA)

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP), have been associated with the use of regorafenib (see section 4.8). The diagnosis of TMA should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. Regorafenib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation.

4.8. Undesirable effects

SOC Blood and lymphatic system disorders:

Thrombotic microangiopathy (frequency rare)

Package leaflet

2. What you need to know before you take Stivarga

Talk to your doctor or pharmacist before taking Stivarga.

Take special care with Stivarga

- If you have or have had damage to the smallest blood vessels (thrombotic microangiopathy (TMA)). Tell your doctor if you develop fever, fatigue, tiredness, bruising, bleeding, swelling, confusion, vision loss, and seizures.

4. Possible side effects

Rare side effects (may affect up to 1 in 1,000 users):

- blood clots in small blood vessels (thrombotic microangiopathy)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Myositis (19882) ⁵	Jean-Michel Dogné (BE)	Assess in the next PSUR (submission by 8 March 2023)	AstraZeneca AB
Elasomeran (COVID-19 mRNA vaccine) - Spikevax	Myositis (19884)	Marie Louise Schougaard Christiansen (DK)	Supplementary information requested (submission by 9 March 2023)	Moderna Biotech Spain, S.L.
Lenvatinib	Adrenal insufficiency (19870)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 9 March 2023)	Eisai GmbH
Progesterone	Meningioma (19871)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 9 March 2023)	Besins Healthcare S.A., Laboratoires Besins International, Besins Healthcare Germany GmbH, Merck A/S
Tozinameran (COVID-19 mRNA vaccine) - Comirnaty	Myositis (19883) ⁵	Menno van der Elst (NL)	Supplementary information requested (submission by 9 March 2023)	BioNTech Manufacturing GmbH
Tozinameran (COVID-19 mRNA vaccine) - Comirnaty	Vulval ulceration (19840)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 27 August 2023)	BioNTech Manufacturing GmbH

⁵ EPITT reference number corrected on 23 June 2023.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; insulin degludec, liraglutide; liraglutide; lixisenatide; insulin glargine, lixisenatide semaglutide	Thyroid cancer (18292)	Mari Thorn (SE)	No action for MAHs at this stage	AstraZeneca AB, Eli Lilly Nederland B.V., Novo Nordisk A/S, sanofi-aventis groupe, Sanofi Winthrop Industrie