6 February 2023[1]
EMA/PRAC/4771/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 9-12 January 2023 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. 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 (EPITT no 19822)

This applies to both single-ingredient and fixed-dose combination products of the concerned substances.

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.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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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 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.

2. Dabrafenib; trametinib – Haemophagocytic lymphohistiocytosis (EPITT no 19824)

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]

~~[a]The 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[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]

~~[a]The 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)~~

~~a~~b Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma
~~b~~c Papilloma, skin papilloma
~~c~~d Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III
~~d~~e Includes drug hypersensitivity
~~e~~f Bleeding from various sites, including intracranial bleeding and fatal bleeding
~~f~~g Abdominal pain upper and abdominal pain lower
~~g~~h Erythema, generalised erythema
~~h~~i 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).

3. Regorafenib – Thrombotic microangiopathy (EPITT no 19832)

Summary of product characteristics

4.4. Special warnings and precautions for use

Thrombotic microangiopathy (TMA)
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopaenic 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

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)