

Drug Safety Update



Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



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A review by EU medicines regulators of clinical studies and cases of suspected adverse drug reactions, reported by healthcare professionals and in the literature, has concluded that trametinib (Mekinist ▼) can cause gastrointestinal perforation or colitis. Trametinib is authorised for unresectable or metastatic melanoma with a BRAF V600 mutation, either as monotherapy or in combination with dabrafenib.

Trametinib should therefore be used with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation – see page 2.

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1 Trametinib (Mekinist ▼): risk of gastrointestinal perforation and colitis

Use trametinib, authorised either as monotherapy or combined with dabrafenib, with caution in patients with risk factors for gastrointestinal perforation.

Advice for healthcare professionals:

- Use trametinib, authorised either as monotherapy or combined with dabrafenib, with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation
- In these patients, be vigilant for signs and symptoms of gastrointestinal perforation. Patients should be advised to seek urgent medical attention if they develop severe abdominal pain
- Suspected adverse reactions to trametinib should be [reported to us on a Yellow Card](#)

Trametinib (Mekinist ▼), authorised as monotherapy or combined with dabrafenib, is indicated for the treatment of adults with unresectable or metastatic melanoma with a BRAF V600 mutation.

Risk of gastrointestinal perforation and colitis

A review by EU medicines regulators of clinical studies and cases of suspected adverse drug reactions, reported by healthcare professionals and in the literature, has concluded that trametinib can cause gastrointestinal perforation or colitis. The review assessed all cases up to 19 November 2015 and identified 4 patients who died from gastrointestinal perforation while receiving trametinib.

Case reports

Of the cases where a causal relation with trametinib (as monotherapy or combined with dabrafenib) was considered likely, most (13 of 19) were reports of gastrointestinal perforation; a few cases reported gastrointestinal perforation with colitis (3) or colitis alone (3). Most cases of gastrointestinal perforation had documented risk factors such as gastrointestinal metastases, diverticulitis, or use of concomitant medicines that can cause gastrointestinal perforation (such as non-steroidal anti-inflammatory drugs or corticosteroids).

Most cases occurred in patients who received trametinib combined with dabrafenib. The risk of these adverse reactions seems to be highest within the first 2 months of starting trametinib, either as monotherapy or combined with dabrafenib.

On the basis of clinical trials of trametinib (as monotherapy), the incidence of colitis or gastrointestinal perforation is approximately 1 in 200.

Potential mechanisms

The inhibitory effects of trametinib on angiogenesis and gastrointestinal epithelial cell proliferation may contribute to the development of gastrointestinal perforation. In patients with gastrointestinal metastases, an additional possible mechanism is rapid tumour shrinkage due to the effects of the trametinib combined with dabrafenib which could result in intestinal perforation at the site of metastases.¹

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1 Kass SL, Linden AF, Jackson, PG. Bowel perforation associated with robust response to BRAF/MEK inhibitor therapy for BRAF-mutant melanoma: a case report. *Melanoma Manag* 2015; 2: 115–20.

2 Letters sent to healthcare professionals in February 2016

In February 2016, a [letter](#) was sent to healthcare professionals regarding valproate, the risk of abnormal pregnancy outcomes and the new communication materials available (see also the [associated Drug Safety Update article](#))

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