



# regorafenib (STIVARGA<sup>o</sup>) and gastrointestinal stromal tumours after treatment failure

## Radiological improvement but major adverse effects

● **Regorafenib** had no impact on overall survival in a placebo-controlled trial in 199 patients, but adverse effects were frequent and serious. Symptomatic care is a more reasonable choice.



NOT ACCEPTABLE

*Imatinib*, an inhibitor of various tyrosine kinases, prolongs survival by a few years in patients with inoperable or metastatic gastrointestinal stromal tumours. *Sunitinib*, another tyrosine kinase inhibitor, is an option if *imatinib* fails. Tailored symptomatic treatment is an alternative (1).

*Regorafenib* (Stivarga<sup>o</sup>, Bayer Pharma) inhibits tyrosine kinases involved in angiogenesis and tumour growth (2). It has been authorised for patients with unresectable or metastatic gastrointestinal stromal tumours after failure of *imatinib* and *sunitinib*.

**No proven survival advantage.** Clinical evaluation of *regorafenib* in this setting is based on a randomised, double-blind, placebo-controlled trial in 199 patients who also received symptomatic treatment (3-5).

Median survival was similar in the two groups, about 17 months (3). Interpretation of this result is difficult as 85% of patients in the placebo group received *regorafenib* when their cancer progressed (3,4). The median time to death or radiological progression (blinded

assessment by an independent committee) was 4.8 months in the *regorafenib* group versus 0.9 months in the placebo group ( $p < 0.0001$ ) (3,4).

**Frequent and often serious adverse effects.** The known adverse effects of *regorafenib* are frequent, often severe and sometimes fatal, including: liver damage; bleeding; hypertension, ischaemic heart disease, cardiac arrhythmia; mucocutaneous damage, including palmoplantar erythrodysesthesia and mucositis; gastrointestinal perforation and fistulae; infections; hypothyroidism; multiorgan hypersensitivity reactions (DRESS); and leukoencephalopathy (2,5,6). *Regorafenib* interacts with many other drugs (2).

This trial provided no additional information on the adverse effect profile of *regorafenib* (3). Serious adverse effects occurred in 61% of patients in the *regorafenib* group and 14% of those in the placebo group. Most of these effects consisted of palmoplantar erythrodysesthesia, hypertension or diarrhoea. Trial investigators attributed three deaths to *regorafenib*: one due to cardiac arrest, one due to acute liver failure, and one due to azotaemia and metabolic acidosis (3).

**In practice.** In patients with unresectable or metastatic gastrointestinal stromal tumours in whom *imatinib* and *sunitinib* have failed, the only proven advantage of *regorafenib* is that it delays radiological progression by about 4 months. *Regorafenib* has no proven impact on overall survival. This improvement in a surrogate endpoint is outweighed by very frequent and often severe adverse effects, resulting in an unfavourable harm-benefit balance.

It is more reasonable to propose symptomatic care rather than expose patients to the adverse effects of *regorafenib*.

### Selected references from Prescrire's literature search.



In response to our request for information, Bayer Healthcare provided us with no documentation on its product.

- 1- Prescrire Editorial Staff "Imatinib and inoperable or metastatic gastrointestinal stromal tumours. Longer follow-up confirms the overall survival benefit" *Prescrire Int* 2011; **20** (114): 61-63.
- 2- Prescrire Editorial Staff "Regorafenib. Metastatic colorectal cancer in treatment failure: may prolong survival by a few weeks" *Prescrire Int* 2014; **23** (145): 8-11.
- 3- EMA - CHMP "Extension of indication variation assessment report for Stivarga. EMEA/H/C/002573/II/0001" 26 June 2014: 62 pages.
- 4- Demetri GD et al. "Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicentre, prospective, randomised, placebo-controlled phase 3 trial (GRID)" *Lancet* 2013; **381** (9863): 17 pages.
- 5- European Commission "SPC-Stivarga" 16 December 2014: 25 pages.
- 6- Prescrire Editorial Staff "Regorafenib: Dress" *Prescrire Int* 2015; **24** (156): 20-21.

### regorafenib tablets

STIVARGA<sup>o</sup>

• 40 mg of regorafenib per tablet

### cytotoxic drug; inhibitor of multiple tyrosine kinases

■ **New indication:** "(...) treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib".

[EU centralised authorisation]

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