Pharmacotherapeutic report, summary

Tegafur/gimeracil/oteracil (Teysuno®) for the indication 'advanced gastric cancer'.
Approved on 24 September 2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Teysuno® hard capsules are available in two strengths. Each capsule contains 15 mg tegafur, plus 4.35 mg gimeracil and 11.8 mg oteracil, or 20 mg tegafur, plus 5.8 mg gimeracil and 15.8 mg oteracil.

Registered indication. For the treatment of advanced gastric cancer in adults when given in combination with cisplatin.

Posology. 25 mg/m^2 (expressed as tegafur content) when administered twice daily, orally, for 21 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every four weeks until disease progression or until intolerable toxicity is observed. The body surface should be recalculated if body weight alters by ≥10%. Comedication: cisplatin 75 mg/m^2 by intravenous infusion administered once every 4 weeks, up to a maximum of 6 cycles.

Mechanism of action. The most important active ingredient in Teysuno® is tegafur, a cycotoxic medicine. Tegafur is a prodrug of 5-fluorocil (5-FU). Following oral administration, tegafur is gradually converted to 5-FU *in vivo*, mainly by CYP2A6 enzyme activity in the liver. 5-FU is metabolised by the liver enzyme DPD and activated within cells by phosphorylation to its active metabolite, 5-fluoro-desoxyuridine-monophosphate (FdUMP). FdUMP and reduced folate are bound to thymidylate synthase, leading to formation of a ternary complex that inhibits DNA synthesis.

The other substances in Teysuno® make tegafur more effective at a lower dose and with fewer side effects: gimeracil (a DPD-inhibitor) inhibits the metabolisation of 5-FU and oteracil (an OPRT-inhibitor) reduces the activity of 5-FU in normal gastrointestinal tract tissues, thereby reducing the toxicity. These substances do not in themselves have any anti-tumour effect.

Summary of the therapeutic value

Intended effects. The combination therapy with epirubicin, a platinum derivative and a fluoropyrimidine, forms the standard regimen for first-line palliative treatment of non-resectable, locally advanced or metastatic gastric adenocarcinoma or carcinoma of the gastro-oesophageal junction in patients with a good health state. The triplet has proven to have a significant survival advantage above a doublet without epirubicin. No study is available that directly compared tegafur/gimeracil/oteracil (as part of the treatment) with the standard treatment. Based on an indirect comparison, tegafur/gimeracil/oteracil, in combination with cisplatin, is less effective than the standard treatment. In a direct comparative study, tegafur/gimeracil/oteracil, in combination with cisplatin, proved just as effective as 5-fluorouracil in combination with cisplatin in adult patients who had not previously received chemotherapy. In an indirect comparison, tegafur/gimeracil/oteracil, in combination with cisplatin, seems just as effective as capecitabine in combination with cisplatin.

Unintended effects. The reported side-effects of using tegafur/gimeracil/oteracil in combination with cisplatin are side effects that are also known to occur with other fluoropyrimidines in

combination with cisplatin. The main ones are myelosuppression and gastrointestinal toxicity. There are no major differences between the side effects of tegafur/gimeracil/oteracil and 5-fluorouracil.

Experience. Experience with tegafur for gastric cancer is limited. Ample experience has been gained with epirubicin, cisplatin and 5-fluorouracil and sufficient experience with capecitabine for this indication.

Applicability. There are no major differences in applicability between tegafur/gimeracil/oteracil and other oncolytics for gastric cancer. This drug is not recommended for people with severe renal impairment and the dose should be reduced for people with a moderate renal impairment.

Ease of use. Most drugs are administered by intravenous infusion. Tegafur/gimeracil/oteracil and capecitabine have the advantage of oral administration. As a result, their use can be continued at home after the infusion of cisplatin.

Final conclusion. The doublet of tegafur/gimeracil/oteracil in combination with cisplatin has a lower therapeutic value in comparison with the standard first-line treatment for non-resectable, locally advanced or metastatic gastric adenocarcinoma or carcinoma of the gastro-oesophageal junction in patients with a good health state. The standard treatment triplet has been proven to have a significant survival advantage in comparison with a doublet without epirubicin. No directly comparative studies are available which prove the effectiveness of tegafur/gimeracil/oteracil in comparison with the standard treatment.

The therapeutic value of tegafur/gimeracil/oteracil, if used in combination with cisplatin, is equal to that of the other fluoropyrimidines, i.e., 5-fluorouracil and capecitabine. Treatment with tegafur/gimeracil/oteracil is just as effective as treatment with 5-fluorouracil, and capecitabine seems to be just as effective as tegafur/gimeracil/oteracil. There are no significant differences in survival advantage between these fluoropyrimidines, nor is there a significant difference in side effects. Tegafur and capecitabine have an advantage in ease of use as these drugs are taken orally.