

tegafur/gimeracil/oteracil 15mg/4.35mg/11.8mg and 20mg/5.8mg/15.8mg
hard capsules (Teysuno®) SMC No. (802/12)

Nordic Pharma Ltd.

10 August 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tegafur/gimeracil/oteracil (Teysuno®) is accepted for restricted use within NHS Scotland.

Indication under review: tegafur/gimeracil/oteracil is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

SMC restriction: tegafur/gimeracil/oteracil is restricted to use in patients with advanced gastric cancer who are unsuitable for an anthracycline, fluorouracil and platinum triplet first-line regimen.

In a multicentre, randomised, open-label clinical study in adult patients with advanced gastric cancer, tegafur/gimeracil/oteracil in combination with cisplatin was non-inferior to an intravenous fluoropyrimidine plus cisplatin with respect to overall survival.

Overleaf is the detailed advice on this product.

**Vice Chairman,
Scottish Medicines Consortium**

Indication

Tegafur/gimeracil/oteracil (Teysono®) is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

Dosing Information

The recommended standard dose of tegafur/gimeracil/oteracil when administered in combination with cisplatin is 25mg/m² (expressed as tegafur content), twice daily, morning and evening, for 21 consecutive days followed by seven days rest (one treatment cycle). This treatment cycle is repeated every four weeks.

Capsules should be taken by mouth with water at least 1 hour before or 1 hour after a meal.

Tegafur/gimeracil/oteracil should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products.

Product availability date

10 April 2012

Summary of evidence on comparative efficacy

Advanced gastric cancer is incurable and the aim of palliative chemotherapy is to increase survival, prevent symptomatic deterioration and improve quality of life. Tegafur/gimeracil/oteracil is formulated as a fixed combination capsule containing tegafur, which is a fluoropyrimidine prodrug of 5-fluorouracil and two enzyme inhibitors: gimeracil and oteracil. Gimeracil reversibly inhibits the catabolism and inactivation of 5-fluorouracil by dihydropyrimidine dehydrogenase, and oteracil inhibits phosphorylation of 5-fluorouracil to 5-fluoridine-5'-monophosphate, the main compound responsible for gastrointestinal toxicity.

The submitting company has asked SMC to consider tegafur/gimeracil/oteracil when positioned for use in patients with advanced gastric cancer who are unsuitable for an anthracycline, fluoropyrimidine and platinum triplet first choice regimen.

The evidence to support the marketing authorisation of tegafur/gimeracil/oteracil derives from one pivotal phase III multicentre, randomised, open-label study to compare overall survival (OS) for cisplatin plus tegafur/gimeracil/oteracil (CS) with cisplatin plus 5-fluorouracil iv (CF) in adult patients with advanced gastric cancer, previously untreated with chemotherapy (FLAGS study).¹ Patients aged ≥18 years with histologically confirmed, unresectable, locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with a performance status of 0 or 1 by the Eastern Cooperative Oncology Group criteria were eligible. A total of 1,053 patients were randomised, 527 in the CS arm and 526 in the CF arm.

In the CS arm, tegafur/gimeracil/oteracil was administered orally at 25mg/m² twice daily for 21 days and cisplatin was administered intravenously at 75mg/m² over one to three hours every 28 days. In the CF arm, 5-fluorouracil was administered at 1000mg/m²/24 hours as an infusion over five days and cisplatin was administered intravenously at 100mg/m² over one to three

hours every 28 days. All patients received hydration and standard prophylactic medication to reduce adverse effects. Cisplatin was discontinued after 6 cycles in both arms and there was provision to continue with tegafur/gimeracil/oteracil or 5-fluorouracil until progression of disease or unacceptable adverse effects. Doses were reduced based on predefined criteria.

The final primary analysis of survival was conducted in the full analysis set, which consisted of all patients who were dosed with study drug (n=521 for CS; n=508 for CF) and included deaths up to 12 months after the last patient was randomly assigned. The median survival of patients in the CS arm was 8.6 months compared with 7.9 months for patients in the CF arm (log-rank P=0.2; hazard ratio (HR) 0.92; 95% confidence interval (CI): 0.80 to 1.05).

Secondary outcomes were overall response rate (ORR), progression-free survival (PFS), time to treatment failure (TTF) and safety. The ORR was 29.1% (n=402) in the CS group and 31.9% (n=385) in the CF group. The PFS was 4.8 months in the CS group and 5.5 months in the CF group; this difference was not statistically significant. The median TTF in both arms was 3.8 months.

Summary of evidence on comparative safety

The dose of cisplatin used in the CS arm (75mg/m²) was lower than that used in the CF group (100mg/m²), which may account for the different frequencies of some of the adverse events between the treatment groups. The percentage of patients who developed at least one treatment-related serious adverse event was lower with CS (20%) than with CF (30%) (p<0.05) and there were significantly fewer renal adverse events and electrolyte imbalances reported with CS compared with CF.

Oteracil is intended to reduce the gastro-intestinal adverse effects associated with 5-fluorouracil. In the FLAGS study, the overall incidence of diarrhoea (29% for CS versus 38% for CF; p<0.01) and the use of anti-diarrhoeal medication (30% for CS versus 49% for CF) were lower in the CS arm. However, the occurrence of grade 3-4 diarrhoea was not significantly different between the two treatment groups (4.8% for CS versus 4.5% for CF).

Overall, the adverse events reported in the FLAGS study were consistent with the known safety profile of fluoropyrimidines and included anaemia (82% for CS versus 78% for CF), nausea (62% for CS versus 67% for CF), vomiting (48% for CS versus 55% for CF [p<0.05]), fatigue (39% for CS versus 39% for CF) and anorexia (32% for CS versus 34% for CF).

There were significantly fewer myelosuppression-related serious adverse events with the CS regimen compared with the CF regimen. Febrile neutropenia/complicated neutropenia was reported in 5% of patients in the CS arm compared with 14% of patients in the CF arm (p<0.01). Grade 3-4 neutropenia occurred in 32% of patients treated with CS compared with 64% of patients treated with CF (p<0.01); grade 3-4 thrombocytopenia occurred in 8% of patients treated with CS compared with 14% of patients treated with CF (p<0.01) and grade 3-4 leucopenia occurred in 14% of patients treated with CS compared with 33% of patients treated with CF (p<0.01).

There were significantly fewer treatment-related deaths with CS (n=13; 2.5%) than with CF (n=25; 4.9%) (p<0.05). There were 4 (0.8%) myelosuppression-related deaths in the CS group and 14 (2.8%) in the CF group (p<0.05).

Hyperbilirubinaemia \geq grade 3 (6.5% for CS versus 3.6% for CF; $p < 0.05$), palmar-plantar erythrodysaesthesia (5.4% for CS versus 2.6% for CF; $p < 0.05$) and increased lacrimation (6.1% for CS versus 1.2% for CF; $p < 0.05$) were all reported significantly more frequently in the CS group.

Summary of clinical effectiveness issues

The pivotal phase III study (FLAGS) demonstrated that tegafur/gimeracil/oteracil in combination with cisplatin (CS) was non-inferior in terms of overall survival to 5-fluorouracil iv in combination with cisplatin (CF) in adult patients with advanced gastric cancer.

The FLAGS study was designed and conducted as a superiority study; however, after completion of the study, the primary objective was switched from superiority to non-inferiority since the final results did not show statistical and clinical evidence for the primary objective: superiority of CS compared with CF.² The non-inferiority margin was considered to have been adequately justified by the European Medicines Agency.²

The median age of patients in the FLAGS study was 59 years, whereas the Scottish Intercollegiate Guidelines Network guideline on the management of oesophageal and gastric cancer states the median age at presentation in Scotland is 72 years.

Published guidelines and information received from clinical experts consulted by SMC indicate that triplet regimens containing an anthracycline with a platinum-based drug and a fluoropyrimidine (e.g. epirubicin, oxaliplatin, capecitabine [EOX]; epirubicin, cisplatin, capecitabine [ECX]) are the current standard chemotherapy regimens used for patients with advanced gastric cancer in Scotland.

There have been no studies investigating the use of tegafur/gimeracil/oteracil in a triplet regimen containing an anthracycline and a platinum-based drug. It was noted by the European Medicines Agency that the efficacy and safety of tegafur/gimeracil/oteracil has not been established in other dosing regimens, including triplet regimens in advanced gastric cancer. Therefore, tegafur/gimeracil/oteracil cannot be considered as a substitute for 5-fluorouracil or other fluoropyrimidines in other combination regimens.²

In the pivotal FLAGS study, there were fewer treatment-related serious adverse events and a lower incidence of vomiting in the CS arm than in the CF arm but this may have been due to the lower dose of cisplatin used in the CS regimen. Oteracil is intended to reduced the gastrointestinal adverse effects of 5-fluorouracil; however, there was no significant difference in the incidence of grade 3-4 diarrhoea between the two groups.

Another orally administered fluoropyrimidine, capecitabine, is accepted for use within NHS Scotland for first line treatment of advanced gastric cancer in combination with a platinum-based chemotherapy regimen. Capecitabine was non-inferior to 5-fluorouracil in terms of overall survival compared with continuously infused 5-fluorouracil when each drug was used in a triplet regimen containing a platinum-based drug and an anthracycline drug.

There has been no direct comparison of tegafur/gimeracil/oteracil with capecitabine. An indirect comparison of the doublet regimens, tegafur/gimeracil/oteracil plus cisplatin¹ (CS) versus capecitabine plus cisplatin⁴ (CX) in advanced gastric cancer was performed using 5-fluorouracil plus cisplatin (CF) as the common comparator. There was no significant difference between the

two arms for overall survival and progression free survival. However, the evidence synthesis has limitations in terms of internal validity, including lack of transparency in study selection, heterogeneity between studies in the doses of cisplatin and 5-fluorouracil used in the common comparator arms, and ethnicity of study populations. The evidence synthesis also has limitations in terms of external validity, as the ability to extrapolate to the population in Scotland may be limited by the high prevalence of Asian patients in the study comparing CX with CF as there is genetic variability in the metabolism of tegafur/gimeracil/oteracil between Asians and Caucasians. A naïve indirect comparison of the adverse event, hand foot syndrome, was also presented by the submitting company but was inconclusive due to lack of robustness.

There was concern that the comparators used in the health economic case (cisplatin plus 5-fluorouracil and cisplatin plus capecitabine) were not appropriate, and it was not clear from the submission whether the company wished SMC to consider tegafur/gimeracil/oteracil in the context of the full licensed indication or when positioned for use in a specific sub-population. However, after the New Drugs Committee meeting, the company clarified that SMC was being asked to consider tegafur/gimeracil/oteracil when positioned for use in patients with advanced gastric cancer who are unsuitable for an anthracycline, fluoropyrimidine and platinum triplet first choice regimen. These patients would currently be treated with a doublet regimen comprising capecitabine with either oxaliplatin or cisplatin.

Tegafur/gimeracil/oteracil is orally administered, so may offer advantages in terms of administration compared with 5-fluorouracil.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis of tegafur/gimeracil/oteracil plus cisplatin (CS) versus either cisplatin and 5-fluorouracil (CF) or cisplatin and capecitabine (CX). The time horizon used was approximately 16 weeks, which equates to 4 cycles of CS and 5.5 cycles of CF and CX, with these durations being based on the median number of cycles from the respective studies. The analysis assumed the following treatment regimes for each arm of the model:

- CF: 5-fluorouracil 800 mg/m² as a continuous infusion over days 1 to 5; cisplatin 80mg/m² as continuous infusion on day 1. A 3-week cycle was assumed.
- CS: tegafur/gimeracil/oteracil 25 mg/m² twice daily for 21 days in a 28-day cycle; cisplatin 75mg/m² as continuous infusion on day 1.
- CX: capecitabine 1000 mg/m² twice daily for 14 days in every 21 days (three-week cycle); cisplatin 80mg/m² as continuous infusion on day 1. A 3-week cycle was assumed.

Clinical data to support the assumed equivalence of treatments necessary for the cost minimisation analysis came from the FLAGS study in the case of the comparison with CF and an indirect comparison in the case of the comparison with CX. Resource use in the model related to drug acquisition costs and drug administration costs. For the CF arm of the model, drug administration included the cost of line insertion (£510) plus the cost of delivering a complex chemotherapy (£318) and the cost of an outpatient follow-up (£292) each cycle.

The following results were obtained:

	CF	CX	CS
Drug administration	£6,588	£2031	£1477
Drug acquisition	£476	£1570	£1344
Total cost	£7,064	£3601	£2821
Cost saving with CS	£4,243	£780	-

Given the findings, CS was assumed to be the preferred treatment on cost-minimisation grounds.

Sensitivity analysis showed that the cost-saving result was robust to changes in a number of key variables or assumptions.

A number of key issues were found with the analysis:

- The justification for the cost-minimisation approach was taken from an indirect comparison and there were some weaknesses with the methodology employed, as noted above.
- For the positioning sought, SMC clinical experts indicated that the comparator regimen of CF is not commonly used in NHS Scotland, and cisplatin plus gemcitabine or oxaliplatin plus capecitabine (OX) are the more relevant doublet comparator treatments.
- There is disparity between the drug regimes that were assumed in the economic model versus what was used in the trials or asserted by the company as being used in clinical practice. However, sensitivity analysis indicated that this did not affect the overall result.
- In some cases, a district nurse may remove the line used for 5FU and thus the cost assumed for an outpatient visit may over-estimate the costs associated. However, sensitivity analysis using different assumptions showed that the cost-saving result remained robust.

In response to the criticism regarding the relevance of the comparators, the company submitted some additional analysis to show the impact of using OX as a comparator. To facilitate this comparison, the company assumed that CS would be as effective as OX on the basis of a published paper which compared triplet regimens containing an anthracycline, a platinum-based drug and a fluoropyrimidine and demonstrated non-inferiority of capecitabine compared with 5-fluorouracil, and of oxaliplatin compared with cisplatin.⁵ The revised analysis also included an option for the CX arm where capecitabine is used at a dose of 625mg/m² continuously for 21 days in a 3-week cycle. Results were presented for time horizons of 12 weeks and 18 weeks and are shown below:

12 weeks*	CX 1000mg	CX 625mg	CS	OX
Drug administration	£1,477	£1,477	£1,108	£1,477
Drug acquisition	£1,142	£1,019	£1,008	£3,539
Total cost	£2,619	£2,496	£2,116	£5,016
Cost saving with CS	£503	£380	-	£2,900

* 3 cycles of CS and 4 cycles of all other regimens

18 weeks*	CX 1000mg	CX 625mg	CS	OX
Drug administration	£2,216	£2,216	£1,662	£2,216
Drug acquisition	£1,713	£1,529	£1,512	£5,308
Total cost	£3,929	£3,745	£3,174	£7,524
Cost saving with CS	£755	£571	-	£4,350

*4.5 cycles of CS and 6 cycles of all other therapies.

These results suggest that CS would be the preferred treatment on cost-minimisation grounds and this remained the case regardless of the price of oxaliplatin. Given the further analyses submitted, the economic case was considered to have been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline 87: Management of oesophageal and gastric cancer (2006) is currently being updated.

Guidelines published in 2011 by the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology recommend that patients with adequate performance status should be considered for combination chemotherapy with EOX (epirubicin, oxaliplatin, capecitabine) or ECX (epirubicin, cisplatin, capecitabine). These guidelines state that until recently, ECF (epirubicin, cisplatin, 5-fluorouracil) was the preferred regimen in the UK. They also say that cisplatin combined with infused 5-fluorouracil (CF) is also commonly used in the UK, and go on to state that, although ECF and CF have not been directly compared in a phase III clinical study, a meta-analysis³ showed that triplet regimens containing anthracyclines, cisplatin and 5-fluorouracil were superior to doublet regimens containing either cisplatin/5-fluorouracil or anthracyclines/5-fluorouracil in terms of overall survival.

The European Society for Medical Oncology guidelines (2010) recommend combination regimens containing a fluoropyrimidine and a platinum agent for patients with metastatic gastric cancer and state that ECF is among the most active and well-tolerated regimens. They also cite the meta-analysis by Wagner and colleagues³ as demonstrating a significant benefit when an anthracycline is added to a platinum- fluoropyrimidine regimen, and go on to describe a clinical study examining the substitution of oxaliplatin (O) for cisplatin (C) and capecitabine (X) for 5-fluorouracil (F), which demonstrated non-inferiority between ECF, ECX, EOF and EOX.

A Canadian clinical practice guideline recommends ECX or ECF for palliative chemotherapy of advanced gastric cancer citing evidence from the study by Cunningham and colleagues.

Additional information: comparators

5-fluorouracil, capecitabine.

Cost of relevant comparators

Regimen	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Tegafur/gimeracil/oteracil plus cisplatin	Tegafur/gimeracil/oteracil 25mg/m ² orally twice daily, on days 1 to 21 of 28 day cycle. Cisplatin 75mg/m ² intravenously on day 1 of 28 day cycle.	331	1984
5-fluorouracil plus cisplatin (dose in FLAGS study)	5-Fluorouracil 1000mg/m ² intravenously on days 1 to 5 of 28 day cycle. Cisplatin 100mg/m ² intravenously on day 1 of 28 day cycle.	196	1176
5-fluorouracil plus cisplatin (dose used in economic analysis)	5-Fluorouracil 800mg/m ² intravenously on days 1 to 5 of 21 day cycle. Cisplatin 80mg/m ² intravenously on day 1 of 21 day cycle.	147	882
Capecitabine plus cisplatin	Capecitabine 1000mg/m ² orally twice daily on days 1 to 14 of 21 day cycle. Cisplatin 80mg/m ² intravenously on day 1 of 21 day cycle.	274	1645

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 08/06/12. Costs for cisplatin from BNF (March 2012). Doses based on body surface area 1.8m². Cost based on 6 cycles.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 48 in years 1 and 5. Based on an estimated uptake of 30% in year 1 (14 patients) rising to 80% in year 5 (38 patients), the gross impact on the medicines budget was estimated at £20k in year 1 rising to £52k in year 5. The net medicines budget impact was estimated as savings of £1.5k in year 1 and a budget impact of £6.3k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Ajani JA, Rodriguez W, Bodoky G et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010; 28: 1547-53.
2. European Medicines Agency. European Public Assessment Report for tegafur/gimeracil/oteracil (Teysono®). 16/10/2010. EMEA/C/001242 www.ema.europa.eu
3. Wagner AD, Grothe W, Haerting J et al. Combination chemotherapies in advanced gastric cancer: An updated systematic review and meta-analysis. J Clin Oncol. 2007; 25 (Suppl18): Suppl Abs. 4555.
4. Kang YK, Kang WK, Shin DB et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009; 20: 666-73.
5. Cunningham D, Starling N, Rao S et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358: 36-46.

This assessment is based on data submitted by the applicant company up to and including 16 July, 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.