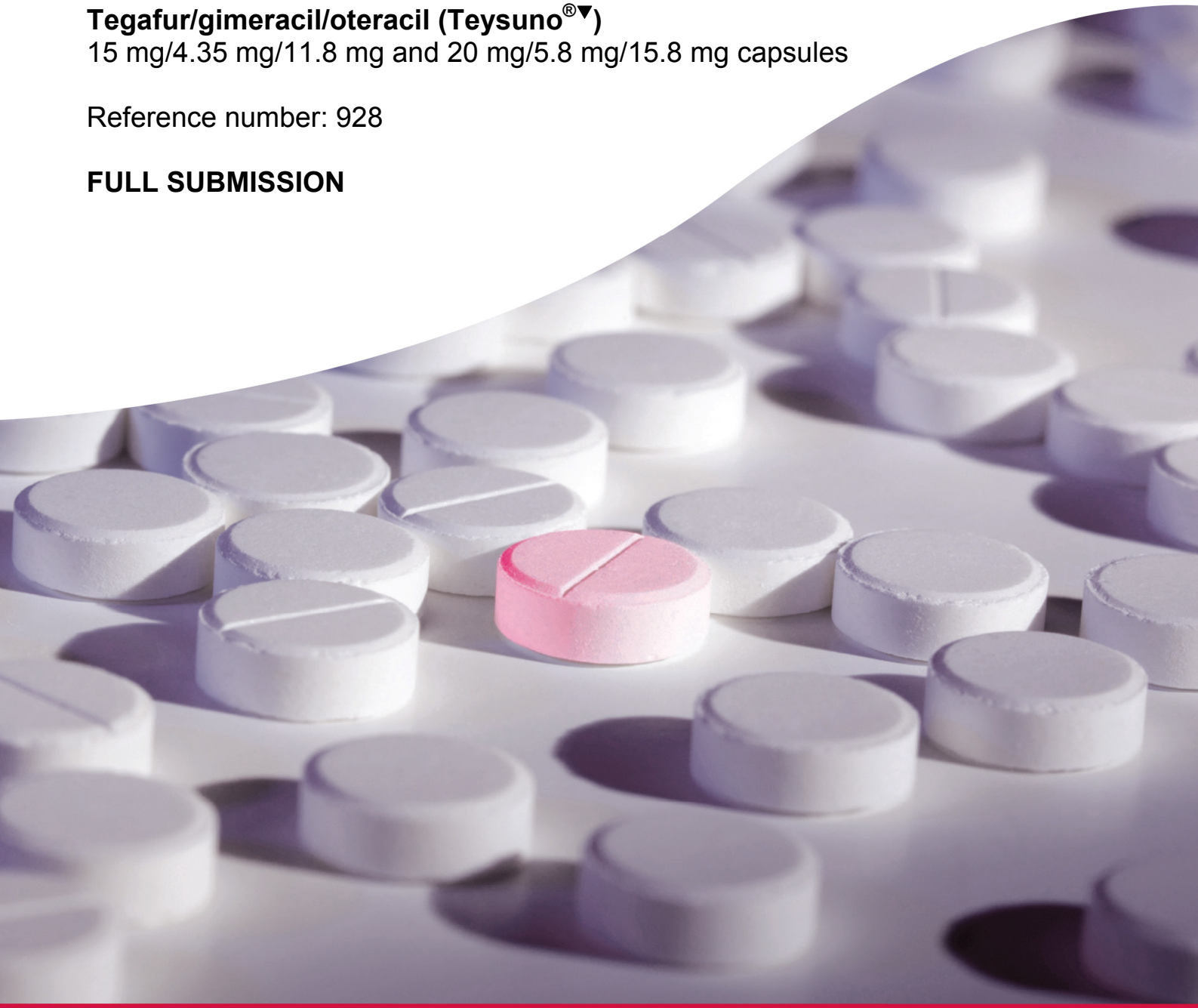
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Tegafur/gimeracil/oteracil (Teysuno®▼)
15 mg/4.35 mg/11.8 mg and 20 mg/5.8 mg/15.8 mg capsules

Reference number: 928

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Tegafur/gimeracil/oteracil (Teysuno®▼)
15 mg/4.35 mg/11.8 mg and 20 mg/5.8 mg/15.8 mg capsules

This assessment report is based on evidence submitted by Nordic Pharma UK Ltd on 6 June 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Tegafur/gimeracil/oteracil (Teysuno®▼) is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin[2,3].
Dosing	The recommended standard treatment cycle of Teysuno®▼ when administered in combination with cisplatin is a twice daily dose of 25 mg/m^2 (expressed as tegafur content), morning and evening, for 21 consecutive days followed by seven days rest. This treatment cycle is repeated every four weeks. The recommended dose of cisplatin with this regimen is 75 mg/m^2 by intravenous infusion administered once every four weeks. Cisplatin should be discontinued after six cycles without withdrawal of Teysuno®▼. If cisplatin is discontinued before six cycles, Teysuno®▼ treatment alone can be resumed when the criteria for restarting it are met. Refer to the Summary of Product Characteristics (SPCs) for further information regarding monitoring and dose modifications, including standard and reduced dosing calculations according to body surface area[2,3].
Marketing authorisation date	14 March 2011[2,3]

2.0 DECISION CONTEXT

2.1 Background

Advanced stage gastric cancer includes locally advanced unresectable gastric cancer (accounting for 30% of cases) and metastatic gastric cancer (accounting for 30% of cases), as well as recurrent gastric cancer after resection[4]. Gastric cancer is the fifth most common cancer in Europe by incidence and the fourth most common cause of cancer-related death[5]. In Wales, the incidence of gastric cancer during 2011 was 471[6] and, as of 31 December 2011, 1,122 patients in Wales had been diagnosed with gastric cancer in the past twenty years[7].

Treatment options for advanced gastric cancer patients in the UK include chemotherapy, which is commonly a triplet regime containing an anthracycline, a platinum agent and a fluoropyrimidine[4,5,8]. Teysuno®▼ is an oral, fixed dose combination of three active substances: tegafur, a prodrug of 5-fluorouracil (5-FU); gimeracil, which prevents degradation of 5-FU through inhibition of the enzyme dihydropyrimidine dehydrogenase; and oteracil, which decreases the activity of 5-FU in

normal gastrointestinal cells through inhibition of orotate phosphoribosyltransferase[2–4]. Teysuno®▼ in combination with cisplatin is indicated in adults for the treatment of advanced gastric cancer[2,3]. The applicant company has suggested that Teysuno®▼ should be considered when standard triplet therapy is not suitable[1].

2.2 Comparators

The comparators included in the company submission were:

- 5-FU intravenous infusion
- Capecitabine (Xeloda®) oral tablets

2.3 Guidance and related advice

- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Gastric Cancer (including cancer in the proximal 5 cm of the stomach) (2013)[9].
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer (2011)[8].
- European Society for Medical Oncology. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2010)[5].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes one phase III study that compared the clinical effectiveness of Teysuno®▼ plus cisplatin with 5-FU plus cisplatin for the treatment of advanced gastric cancer (FLAGS trial). The company submission also references a study that compared capecitabine plus cisplatin and 5-FU plus cisplatin (study ML17032) and this allows a qualitative indirect comparison of Teysuno®▼ plus cisplatin and capecitabine plus cisplatin for the treatment of advanced gastric cancer[1].

3.1 Comparative efficacy

3.1.1 FLAGS study

This phase III, multicentre, randomised, open-label, parallel group, active-controlled trial evaluated the efficacy and safety of Teysuno®▼ plus cisplatin in comparison with 5-FU plus cisplatin for the treatment of patients with advanced gastric cancer previously untreated with chemotherapy for advanced disease[4,10]. Patients (n = 1,053) were randomised (1:1) to one of two treatment groups: Teysuno®▼ (25 mg/m^2 administered twice daily for 21 consecutive days followed by a seven-day recovery period); or 5-FU (1,000 mg/m^2/24 hours administered by continuous intravenous infusion over 120 hours [days 1–5], with repeat doses every 28 days). Patients also received cisplatin as an intravenous infusion on day 1, repeated every 28 days (75 mg/m^2 in the Teysuno®▼ arm and 100mg/m^2 in the 5-FU group). Cisplatin was discontinued after six cycles in both arms but patients could continue Teysuno®▼ or 5-FU until progression of disease or unacceptable toxic effects. The median duration of treatment was approximately 18 weeks and four treatment cycles[4,10].

The study enrolled patients (≥ 18 years) with histological confirmed, unresectable, locally advanced (Stage IV) or metastatic gastric cancer, including adenocarcinoma of the gastro-oesophageal junction and no prior cytotoxic chemotherapy for advanced gastric cancer. Additionally, eligible patients had an Eastern Cooperative Oncology Group Scale (ECOG) performance status of 0 or 1 (see Glossary)[4,10].

The primary endpoint was overall survival (OS) in the full analysis set population, while secondary endpoints included overall response rate (ORR) and progression free survival (PFS); see Glossary for endpoint definitions[4,10]. The study was designed and conducted as a superiority study; however, the investigators considered it appropriate

to switch the primary objective from superiority to non-inferiority after completion of the study, using a company-derived non-inferiority margin of 1.10 in the hazard ratio (HR) scale.

The median OS was 8.6 months in the Teysuno®▼ group, compared with 7.9 months in the 5-FU group (hazard ratio [HR]: 0.92; 95% confidence interval [CI]: 0.80–1.05)[4,10]. The Committee on Human Medicinal Products (CHMP) considered that the criteria for non-inferiority was met[4]. This was supported by analysis of secondary endpoints, including PFS (see Table 1) and ORR (117/402 [29.1%] Teysuno®▼ group versus 123/385 [31.9%] 5-FU group; 95% CI: −9.3–3.6).

Table 1. Overview of indirect comparison data.

	Median OS	Median PFS
FLAGS study (full analysis set population)[4,10]		
Teysuno®▼ plus cisplatin (n = 521)	8.6 months	4.8 months
5-FU plus cisplatin (n = 508)	7.9 months	5.5 months
Hazard ratio (HR)	0.92 (95% CI: 0.80–1.05)	0.99 (95% CI: 0.86–1.14)
Study ML17032 (intent-to-treat population)[11]		
capecitabine plus cisplatin (n = 160)	10.4 months	5.6 months
5-FU plus cisplatin (n = 156)	8.9 months	5.0 months
Hazard ratio (HR)	0.85 (95% CI: 0.65–1.11)	0.80 (95% CI: 0.63–1.03)

3.1.2 Indirect comparison

The applicant company referenced a phase III, multicentre, randomised, open-label, active-controlled study that evaluated capecitabine plus cisplatin against 5-FU plus cisplatin in the treatment of patients with advanced gastric cancer (study ML17032)[1,11]. Patients (n = 316) were randomised (1:1) to receive cisplatin (80 mg/m^2 as a two-hour intravenous infusion on day 1) with either capecitabine (1,000 mg/m^2 twice daily on days 1–14 every three weeks) or 5-FU (800 mg/m^2/24 hours administered by continuous intravenous infusion on days 1–5 every three weeks)[11].

The study enrolled patients (18–75 years) with histological confirmed measurable advanced gastric cancer and no prior chemotherapy for advanced gastric cancer. Additionally, eligible patients had a Karnofsky performance status of at least 70 (see Glossary)[11].

The primary endpoint was PFS in the per protocol population and median PFS was 5.6 months in patients that received capecitabine plus cisplatin and 5.0 months in those that received 5-FU plus cisplatin (HR: 0.81; 95% CI: 0.63–1.04); this met the pre-specified criteria for non-inferiority. Secondary endpoints included OS and objective response rate in the per protocol population. Similar data was observed in the intent-to-treat population (see Table 1)[11].

In the absence of direct evidence for Teysuno®▼ plus cisplatin versus capecitabine plus cisplatin, the applicant company made a qualitative indirect comparison between the FLAGS study and the ML17032 study, utilising the 5-FU plus cisplatin groups as a reference arm (see Table 1). The applicant company concluded that it is logical and appropriate to consider Teysuno®▼ plus cisplatin therapy equivalent to capecitabine plus cisplatin[1].

3.2 Comparative safety

Comparative safety evidence for Teysuno®▼ plus cisplatin versus 5-FU plus cisplatin was reported in the FLAGS study[10]. The overall incidence of patients reporting adverse events (AEs) during this study was 514/521 (98.7%) in Teysuno®▼-treated

patients and 504/508 (99.2%) in the 5-FU group, and of these 92.1% and 95.7% were considered treatment-related, respectively[4]. There were fewer treatment-related serious AEs (SAEs) reported in the Teysuno®▼ group compared to the 5-FU group (20.5% versus 29.7%). Similarly, incidence of discontinuation due to AEs was 56 (10.7%) in the Teysuno®▼ group and 73 (14.4%) in the 5-FU group and the incidence of death due to toxicity was 13 (2.5%) and 25 (4.9%), respectively. Deaths related to myelosuppression were observed in 0.8% of the Teysuno®▼ plus cisplatin group versus 2.8% in the 5-FU plus cisplatin arm ($p < 0.05$)[4].

The most frequently reported AEs in Teysuno®▼-treated patients included nausea (61.6% of Teysuno®▼ group versus 67.3% of 5-FU group), vomiting (48.0% versus 55.3%, respectively), anaemia (44.0% versus 46.1%), fatigue (39.3% versus 39.4%), anorexia (31.5% versus 34.4%), diarrhoea (29.2% versus 38.4%), neutropenia (28.6% versus 47.2%), weight decrease (28.4% versus 32.3%), abdominal pain (25.1% versus 22.4%), thrombocytopenia (17.7% versus 22.8%) and leukopenia (17.5% versus 23.0%)[12]. While most AEs occurred more frequently in 5-FU-treated patients, significantly more patients in the Teysuno®▼ group reported palmar-plantar erythrodysesthesia (5.4% versus 2.6%), increased lacrimation (6.1% versus 1.2%) and grade ≥ 3 hyperbilirubinaemia (6.5% versus 3.6%)[4,12].

CHMP accepted that Teysuno®▼ plus cisplatin was a safe alternative chemotherapy regimen for the treatment of patients with advanced gastric cancer and considered that the AEs reported in the FLAGS study were in accordance with the class and mechanism of action of the medicines, as well as the baseline characteristics of the study population[4]. No data are available for comparing the safety of Teysuno®▼ plus cisplatin and capecitabine plus cisplatin.

3.3 AWTTC critique

- The applicant company has suggested that Teysuno®▼ should be considered when standard triplet therapy is not suitable[1]. At the time of licensing, CHMP considered that the clinical efficacy of Teysuno®▼ was established in combination with cisplatin for the treatment of advanced gastric cancer where fluoropyrimidine plus cisplatin doublet therapy is indicated, but that it has not been established in other dosing regimens or combinations, including triplet therapy for advanced gastric cancer[4]. Teysuno®▼ therefore, was only approved as a double-regimen with cisplatin[4].
- In the FLAGS study the eligibility criteria and baseline characteristics of enrolled patients did not identify factors that would preclude use of triplet therapy regimens[10]. It is therefore uncertain whether the population enrolled in the study reflects the use of Teysuno®▼ where standard triplet therapy is not suitable.
- The company submission includes a direct comparison between Teysuno®▼ plus cisplatin and 5-FU plus cisplatin and a qualitative indirect comparison with capecitabine plus cisplatin[1]. These studies differed with regard to inclusion and exclusion criteria, disease severity and baseline population characteristics[10,11]. In addition, the 5-FU plus cisplatin dosing regimen utilised in the control arm of the studies differed between the studies, limiting the extent to which this can be used as a reference arm. Furthermore, the studies differed with regard to ethnicity of enrolled patients, as 66.1% of patients enrolled in the ML17032 study were Asian, compared with 0.8% in the FLAGS study[10,11]. Due to these differences in methodology and patient population (see Section 3.1.2), the findings of the indirect comparison should be interpreted with caution.
- At the time of licensing, CHMP noted that oral fluoropyrimidines, such as capecitabine, have nowadays largely replaced 5-FU continuous infusion in the treatment of advanced gastric cancer due to improved tolerability and convenience, and there are some data to suggest possible improved efficacy[4]. CHMP also suggested that the 5-FU plus cisplatin schedule selected as control

treatment for the FLAGS study may not be considered anymore as an optimal treatment.

- The FLAGS study was designed and conducted as a superiority study; however, the final results of the trial did not show statistical and clinical evidence for the primary objective of superiority of Teysuno®▼ plus cisplatin over 5-FU plus cisplatin. The investigators considered it appropriate to switch post-hoc, after completion of the study, the primary objective from superiority to non-inferiority, discussing the criteria in accordance with the CHMP guideline, Points to Consider on Switching between Superiority and Non-inferiority[4]. CHMP considered the non-inferiority margin to have been adequately justified, and concluded that Teysuno®▼ plus cisplatin had been demonstrated to be non-inferior to 5-FU plus cisplatin with regard to OS, response rate and PFS[4].
- During the FLAGS study, Teysuno®▼-treated patients received a cisplatin dose of 75 mg/m^2 while patients in the 5-FU group received a 100 mg/m^2 cisplatin dose[10]. When considering the study, CHMP expressed a concern that an increased incidence of toxicity-related mortality and discontinuations in the 5-FU plus cisplatin group due to a higher cisplatin dose could have contributed to an overestimation of efficacy and safety of Teysuno®▼ plus cisplatin[4]. To address this, additional sensitivity analyses were undertaken to assess the potential effect of myelosuppression-related events. CHMP concluded that it was unlikely that the increased myelosuppression-related deaths/discontinuations in patients that received 5-FU plus cisplatin impacted on the non-inferiority of Teysuno®▼ compared to 5-FU[4].
- In Wales, the median age of patients at stomach cancer diagnosis is 72.7 years[13]. However, the median age of patients treated during the FLAGS study was 59.0 years, and only 14.2% of these patients were aged ≥ 70 years[4]. While there is no evidence to suggest that Teysuno®▼ would be less effective in older patients, no subgroup analysis of this population is available. Further, the incidence of several AEs (including leukopenia, neutropenia, thrombocytopenia, diarrhoea, asthenia, hypokalaemia and hyponatraemia, disease progression and dehydration) was greater (≥ 5% difference) in older patients that received Teysuno®▼ than in younger patients within the same treatment group[4]. It is uncertain how this would affect effectiveness in clinical practice in Wales.
- Teysuno®▼ and capecitabine are administered as twice daily oral formulations[2,3], whereas 5-FU for the treatment of advanced gastric cancer is administered as a continuous intravenous infusion[5], with the attendant risk of complications, and requiring hospital admission, which may impact on patient preference.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost minimisation analysis (CMA) of Teysuno®▼ 25 mg/m^2 twice daily for 21 days in combination with cisplatin 75 mg/m^2 as continuous intravenous infusion on day 1 of a four-week cycle compared against four other doublet regimens for the treatment of adults with advanced gastric cancer:

- 5-FU 800 mg/m^2/day as a continuous intravenous infusion over days 1 to 5 plus cisplatin 80 mg/m^2 as continuous intravenous infusion on day 1 of a three-week cycle (CF)
- Oral capecitabine 1000 mg/m^2 twice daily for 14 days plus cisplatin 80 mg/m^2 as continuous intravenous infusion on day 1 of a three-week cycle (CX1)
- Oral capecitabine 625 mg/m^2 twice daily for 21 days plus cisplatin 60 mg/m^2 as continuous intravenous infusion on day 1 of a three-week cycle (CX2)
- Oral capecitabine 625 mg/m^2 twice daily for all 21 days of a three-week cycle plus oxaliplatin 130 mg/m^2 as continuous intravenous infusion on day 1 (OX).

The analysis is restricted to the use of the Teysuno®▼ when a standard triplet regimen (e.g. anthracycline, platinum and fluoropyrimidine) is not suitable.

For the comparison of Teysuno®▼ plus cisplatin against CF, the company assumed therapeutic equivalence based on the results of the phase III FLAGS trial[10] (see Sections 3.1.1 and 3.3), which demonstrated that OS with the above Teysuno®▼ regimen was non-inferior to that with 5-FU administered at 1000 mg/m^2/day over five days plus cisplatin administered at 100 mg/m^2 on day 1 of a four-week cycle (i.e. a different CF regimen to that above). For the comparison against the CX1 and CX2 regimens, the company assumed therapeutic equivalence based on the results of study ML17032, which found CX1 to be non-inferior to CF (regimens as in the company CMA) for PFS and OS[11]. For the comparison against OX, the basis of the assumption of therapeutic equivalence is not provided.

Drug acquisition costs were based on the minimum price per mg as listed in the British National Formulary (BNF) 65 and assuming an average body surface area of 1.75m^2. Drug administration costs were based on schedules observed in the above trials, with unit costs based on NHS Reference Costs for 2011/2012. It is assumed in the base case analysis that pharmacy preparation costs are equal for all regimens, as are the costs of first dose administration. The CF regimen incurs additional costs for initial line insertion, and follow up administration. For all regimens, 20% of patients are assumed to require NHS transportation per administration. AEs are assumed equal across regimens and attract no costs. The submission provides cost estimates over 18 weeks, in line with the median duration of therapy in the FLAGS trial[10], equivalent to 4.5 four-week cycles for Teysuno®▼ plus cisplatin and six three-week cycles for all other regimens.

4.1.2 Results

The results of the base case analysis are presented in Table 2. Teysuno®▼ plus cisplatin was the least costly of all the regimens considered.

Table 2. Costs of Teysuno®▼ and comparator regimens over 18 weeks[1].

Costs	Teysuno®▼ plus cisplatin	CF	CX1	CX2	OX
Drug acquisition	£1,512	£519	£1,712	£1,529	£5,308
Drug administration	£1,743	£4,630	£2,324	£2,324	£2,324
Total cost	**£3,255**	**£5,149**	**£4,037**	**£3,853**	**£7,632**
Cost difference vs Teysuno®▼ plus cisplatin		£1,894	£782	£598	£4,377
CF: cisplatin plus 5-FU; CX: cisplatin plus capecitabine; OX: oxaliplatin plus capecitabine.					

Sensitivity and scenario analyses include alternative drug administration costs and assumptions of CF follow-up visit costs. In all analyses explored, the Teysuno®▼ regimen remained the least costly with the exception of exclusion of line insertion costs and replacing outpatient visits to district nurse visits, which reduced the total costs of the CF regimen to £3,230. Inclusion of AE costs did not greatly influence the results.

4.1.3 AWTTC critique

The reliability of the CMA presented by the company is dependent upon the extent to which the Teysuno®▼ regimen is considered to have been demonstrated to be therapeutically equivalent to the relevant comparators. There is a lack of direct comparative data for the Teysuno®▼ regimen and the CX1, CX2 and OX regimens. A qualitative judgment on the indirect comparison of the results from the FLAGS trial and one trial of the CX1 regimen has been conducted. The basis of selection of that one trial is not stated and there are some potentially important sources of heterogeneity in

the patient populations and the treatment regimens. The company has not submitted evidence relating to any quantitative, adjusted indirect comparison and collectively, there appears to be a high level of uncertainty in the assumption of therapeutic equivalence. The costing approach appears conservative, and the model is robust to changes in the cost assumptions; however, the CMA approach precludes exploration of uncertainty in all but costs.

Strengths of the economic evidence:

- Direct comparative data are available for the comparison of the Teysuno®▼ and the CF regimens, and the company has adopted conservative costing assumptions for the CF regimen.
- A range of sensitivity and scenario analyses have been conducted to explore several costing assumptions.

Limitations of the economic evidence:

- The economic evidence presented by the company relates only to a subset of the licensed indication when a standard triplet regimen is not appropriate.
- The only direct comparative data relate to the CF regimen, which CHMP notes may no longer be considered an optimal treatment regimen in these patients[4].
- There is a lack of direct comparative data for the Teysuno®▼ regimen and the CX1, CX2 and OX comparator regimens. The submission refers to indirect comparison of trial data but no formal data synthesis has been attempted. There are no details of a systematic literature review to identify relevant trials to inform an indirect comparison and the basis of selection of the trial providing a comparison of CX1 and CF is not stated. There are some potentially important differences in the patient populations and the drug regimens received, which limit the conclusions that may be drawn. No basis for the assumption of therapeutic equivalence for the Teysuno®▼ and the OX regimens is provided, and AWTTC-sought expert opinion suggests this may be one of the more relevant comparator regimens.
- The CMA framework assumes equivalence in all domains of health outcomes, which precludes exploration of the differences that may exist in health-related quality of life.
- The drug acquisition costs are estimated on a per mg basis, which suggests no wastage. This assumption has not been explored in the model; however, the main driver of cost differences relates to administration costs.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) have not identified any published evidence on the cost-effectiveness of Teysuno®▼ within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on data from the Welsh Cancer Intelligence and Surveillance Unit for 2001–2011, the company estimates that the incidence of advanced gastric cancer is decreasing by an average of 13 patients per year[1]. From a figure of 591 in 2001, the company estimates there will be 423 in 2012, decreasing to 370 in 2016. As overall survival is typically less than 12 months, the company assumes incident figures approximate to prevalence figures. It is assumed that 25% of patients would receive chemotherapy within six months of diagnosis, and it is estimated that uptake would increase linearly from 10% of patients in the first year to 50%. The total cost estimates from the CMA are used to estimate net budget impact, assuming that the displaced treatment regimens are a mean average of the costs of CF, CX1 and OX regimens.

5.1.2 Results

Table 3 presents the budget impact estimates as presented in Section 8 of the company submission[1].

Table 3. Company-reported costs associated with doublet regimens[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication(s) covered in this submission)	12	12	11	11	11
Uptake (%)	10	20	30	40	50
Treated patients	1	2	3	4	5
Net costs (assuming 1/3 each CX,CF and OX)					
Administration and monitoring	−£1,272	−£2,543	−£3,815	−£5,087	−£6,358
Secondary & tertiary care	−£976	−£1,952	−£2,929	−£3,905	−£4,881
Overall net cost	−£2,248	−£4,496	−£6,744	−£8,992	−£11,239

5.1.3 AWTTC critique

- These budget impact estimates are based on the costs assumed in the base case CMA. Any uncertainties and limitations of the economic evidence highlighted in Section 4.1.3 therefore also apply to the budget impact analysis. Moreover, the net financial costs of introducing Teysuno®▼ in practice may not be equivalent to the opportunity costs calculated for the economic analysis.
- It is simply assumed that current treatment regimens are split evenly between the CF, CX1 and OX regimens, which seems unlikely, given that the CF regimen may no longer be considered an optimal treatment regimen and the large cost differentials.
- Collectively there is a good deal of uncertainty in the company's budget impact estimates in terms of patient numbers, uptake and costs of existing treatment regimens. However, under the assumption of the CMA in Section 4, the company anticipates cost savings from the use of Teysuno®▼, irrespective of the number of eligible patients or displaced regimens.

5.2 Table of comparative unit costs

Table 4 provides example comparative acquisition costs for doublet treatment regimens based on 18 weeks of treatment (as per the median duration of treatment in the FLAGS trial[10]). This equates to 4.5 cycles of treatment with the Teysuno®▼ regimen and the CF regimen used in the FLAGS trial and 6 cycles for all other regimens.

Table 4. Examples of doublet treatment regimen costs in treatment of advanced gastric cancer.

Treatment regimen	Example dose regimen	Approximate cost per cycle*	Approximate cost per 18 weeks*
Teysuno®▼ + cisplatin	Teysuno®▼ 25 mg/m^2 twice daily for 21 days in combination with cisplatin 75 mg/m^2 as continuous IV infusion on day 1 of a four-week cycle	£346	£1,556
5-FU + cisplatin (CF as in company submission)	5-FU 800 mg/m^2/day as a continuous IV infusion over days 1 to 5 plus cisplatin 80 mg/m^2 as continuous IV infusion on day 1 of a three-week cycle	£164	£985
5-FU + cisplatin (CF as in FLAGS trial)	5-FU 1000 mg/m^2/day as a continuous IV infusion over days 1 to 5 plus cisplatin 100 mg/m^2 as continuous IV infusion on day 1 of a four-week cycle	£205	£923
Capecitabine + cisplatin (CX1)	Capecitabine 1000 mg/m^2 twice daily for 14 days plus cisplatin 80 mg/m^2 as continuous IV infusion on day 1 of a three-week cycle	£272	£1,633
Capecitabine + cisplatin (CX2)	Capecitabine 625 mg/m^2 twice daily for 21 days plus cisplatin 60 mg/m^2 as continuous IV infusion on day 1 of a three-week cycle	£257	£1,547
Capecitabine + oxaliplatin (OX)	Capecitabine 625 mg/m^2 twice daily for all 21 days of a three-week cycle plus oxaliplatin 130 mg/m^2 as continuous IV infusion on day 1	£905	£5,430

*Costs based on BNF list prices as of 06 July 2013[14], assuming the lowest cost per mg and a body surface area of 1.8m^2. Excludes reconstitution costs and assumes no wastage
This table does not imply therapeutic equivalence of the medicines and doses listed.
See all relevant SPCs for full dosing details[2,3,15–17].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, tegafur/gimeracil/oteracil (Teysuno®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that tegafur/gimeracil/oteracil (Teysuno®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted one ongoing study that is likely to be available within 6–12 months: a phase I study establishing the dose of Teysuno®▼ as part of a triplet regimen with epirubicin and oxaliplatin[1].

Standard literature searches conducted by AWTTC identified a phase II trial comparing capecitabine plus cisplatin and Teysuno®▼ plus cisplatin as first line treatment for advanced gastric cancer[18]. The company note that this is being carried out in Japan and therefore the patient population and treatment regimens differ to those in Wales.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 27 June 2013
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Eastern Cooperative Oncology Group (ECOG) performance status score
A scale from 0 to 5, where: 0 indicates that the patient is fully active and able to undertake all pre-disease activities without restriction; 1 indicates the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 indicates that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities[19].

Karnofsky performance status
A standard way of measuring the level of patient activity and ranges from 0 to 100, where a higher score means that the patient is better able to carry out daily activities[20].

Overall survival (OS)
OS is defined in the FLAGS study and the ML17032 study as the time from randomisation to death due to any cause[10,11].

Progression free survival (PFS)
PFS is defined in the FLAGS study and the ML17032 study as the time from randomisation to date of first documented progression of disease or date of death[10,11].

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