Scottish Medicines Consortium

tigecycline 50mg vial of powder for intravenous infusion (Tygacil®) (277/06)

Wyeth

9 June 2006

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

Tigecycline (Tygacil®) is accepted for restricted use within NHS Scotland for the treatment of complicated intra-abdominal infection.

Tigecycline is associated with clinical cure rates in patients with complicated intra-abdominal infections non-inferior to those with a broad-spectrum beta-lactam antibiotic. It is restricted to 2nd line use under the advice of local microbiologists or specialists in infectious disease.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Tigecycline 50mg powder for intravenous infusion (Tygacil®)

Indication

Treatment of complicated intra-abdominal infections. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Dosing information

100mg, then 50mg every 12 hours by intravenous infusion over 30-60 minutes.

UK launch date

May 2006

Comparator medications

Drugs from a variety of pharmacological classes are licensed as parenteral preparations for the treatment of intra-abdominal infections in the UK. The current, 51st, edition of the British National Formulary suggests that peritonitis may be initially treated with a cephalosporin (or gentamicin) plus metronidazole (or clindamycin). In Scottish practice empiric treatment of intra-abdominal infections commonly comprises a cephalosporin, such as cefotaxime, and metronidazole. Other options for these types of infection include piperacillin/tazobactam or a carbapenem (meropenem or imipenem) either alone or with metronidazole. When infection is caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin or teicoplanin are often used and for infections caused by bacteria that produce extended spectrum β-lactamases (ESBL) carbapenems may be used.

Cost of relevant comparators

Antibiotic Regimen	Daily dose	Cost per course (£)*
Tigecycline	**100mg, then 50mg twice daily**	**355-937**
Meropenem	0.5-1g three times daily	215-1203
Imipenem-cilastatin	500mg two to four times daily	180-672
Piperacillin-tazobactam	4.5g three times daily	237-663
Cefotaxime plus Metronidazole	1-2g three times daily 500mg three times daily	116-503
Vancomycin	1g twice daily	130-364

Costs from eVadis drug dictionary accessed on 30th March 2006 and based on a course of 5-14 days; all drugs are given intravenously; * adding gentamicin 100-160mg twice daily would increase the cost of a course by £31-86; adding metronidazole 500mg three times daily would increase the cost of a course by £51-143.

Summary of evidence on comparative efficacy

Tigecycline, a glycylcycline, is a tetracycline antibacterial that binds to bacterial ribosomal subunit 30S and inhibits protein synthesis within bacteria. It is not affected by some bacterial mechanisms of tetracycline-resistance, such as ribosomal protection and efflux, therefore it may be active against some bacteria that are resistant to other tetracyclines.

Two double-blind trials recruited adults who had or required a laparotomy, laparoscopy or percutaneous drainage of an intra-abdominal abscess for treatment of a complicated intra-abdominal infection (cIAI) and had an acute physiology and chronic health evaluation (APACHE) II score ≤30. They had received not more than one dose of non-study antibiotic after the baseline culture was taken from the site of infection and were randomized, with stratification for APACHE II score (≤15 or 16-30), in a 1:1 ratio to tigecycline 100mg then 50mg every 12 hours by intravenous (iv) infusion or imipenem-cilastatin 500mg/500mg iv infusion every 6 hours. The dose of the latter drug could be adjusted on the basis of weight and creatinine clearance as specified in the Summary of Product Characteristics (SPC). The primary outcome, clinical cure at test-of-cure (TOC) visit 12-42 days after the last dose of study drug was primarily assessed in the microbiological-modified-intention-to-treat (m-mITT) and the microbiologically evaluable (ME) populations. These comprised all randomised patients who received at least one dose of study drug, had clinical evidence of infection and a pathogen isolated from the baseline culture, with the ME population also excluding patients who had an indeterminate response at the TOC visit. Clinical cure at TOC, assessed by a blinded investigator and defined as resolution of cIAI, was achieved by 74% and 78% of patients in the m-mITT population of the first trial who were given tigecycline and imipenem-cilastatin, respectively, and by 81% and 82% of the ME population in the respective treatment arms. The corresponding results in the other trial were 87% and 85% of the m-mITT population and 91% and 90% of the ME population. In both studies, non-inferiority of tigecycline to imipenem-cilastatin, predefined as a lower limit of the 95% confidence interval (CI) for the difference (tigecycline minus imipenem-cilastatin) in these clinical cure rates of -15% or greater, was demonstrated.

In a combined analysis of these trials microbiological response rates, defined as eradication of baseline isolate at the TOC visit, with tigecycline and imipenem-cilastatin mirrored the clinical cure rates in the ME population, 86% in both groups, with 95% CI for the difference of -4.5% to 4.4%. In this analysis and in the individual studies tigecycline was found to be non-inferior to imipenem-cilastatin for this outcome. Eradication rates at the test-of-cure visit for the most commonly isolated intra-abdominal pathogens were similar in the two treatment groups, with no significant differences between them.

Summary of evidence on comparative safety

In a pooled analysis of the two trials described previously tigecycline was associated with significantly more treatment-emergent gastrointestinal adverse events than imipenem-cilastatin, 44% vs. 39%, mainly nausea (24% vs. 19%) and vomiting (19% vs. 14%), which were generally mild to moderate. Tigecycline was associated with significantly more reports of infection as a treatment-emergent adverse event, 10% vs. 5.5%, and significantly more reports of leucocytosis, 4.4% vs. 2.4% and hypoproteinaemia, 5.9% vs. 3.6%. Tigecycline, compared to imipenem-cilastatin, was associated with significantly fewer patients reporting treatment-emergent adverse events of headache (3.4% vs. 5.8%) and phlebitis (2.0% vs. 4.0%).

Summary of clinical effectiveness issues

Patients from the UK were recruited at 2 of 94 centres participating in one of the trials described. It is not possible to determine from the data available whether there are any differences between the Scottish population and the total trial populations in factors such as, bacterial resistance patterns, healthcare services, prevalence of co-morbidities or levels of performance status (e.g. almost all patients in the studies described previously had an APACHE II score $\leq$15) which would affect the size of clinical benefits to be expected with tigecycline in Scottish clinical environments where it might be used.

In the trials described previously tigecycline was compared to imipenem-cilastatin, which is not the routine empiric treatment for IAIs in Scottish practice, although it can be used for the treatment of IAIs, especially those resistant to other antibiotics. In a combined analysis of the trials described previously, approximately half of the patients had complicated appendicitis and a further 14% has complicated cholecystitis. It appears that many patients had not received any previous antibiotics for treatment of their IAI. It is possible that many of the IAIs in these trials could have been treated with antibiotic regimens used for initial therapy of IAIs in Scottish practice, such as cefotaxime and metronidazole. There are no direct comparisons of tigecycline with these antibiotic regimens. Therefore, efficacy and safety of tigecycline relative to these regimens are unknown.

In the trials described previously a limited number of pathogens resistant to other antibiotics were isolated. In the tigecycline group there were 4 MRSA, 9 ESBL-producing *Escherichia coli* and 6 ESBL-producing *Klebsiella pneumoniae* isolated. Tigecycline was associated with bacterial eradication for 3 (75%) of the MRSA and 12 (80%) of the ESBL-producing bacteria. Although there are limited clinical data on the treatment of infections caused by bacteria resistant to other antibiotics, such as MRSA, *in vitro* studies indicate that tigecycline may be effective in the treatment of these types of infections.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility analysis that showed using tigecycline was likely to be cost effective for about 52% of the times it is used as 2nd or as 3rd line, assuming a willingness to pay of £20,000 per quality adjusted life year (QALY).

The model compared tigecycline to four comparators for a nine different pathogens. Patients enter the model after failing 1st line therapy; if 2nd line antimicrobial treatment fails a 3rd treatment is provided. On completion of 3rd line therapy it is assumed that 50% of patients whose infections have not cleared will die, whilst 50% move on to 4th line therapy. Following 4th line therapy it is assumed 80% of patients with non-eradicated infection die and the rest resolve (of 1,000 patients 1 patient dies). The only costs included are drug costs and additional length of hospitals stays for patients with infections that fail to resolve. Patients who survive are attributed a QALY based on mean life expectancies and utility values for the general population for the relevant age group. Tigecycline is used as 2nd or 3rd line therapy in the treatment sequence.

The modelling results were reported as the probability a regimen including tigecycline has the highest net benefit at a given cost per QALY threshold. Sensitivity analyses were limited to the adoption of a different resistance curve.

The main weakness with the submission is that the clinical effectiveness data are not from use as a 2nd or 3rd line therapy, but rather as first line. The manufacturer has advised that

they assumed that each antimicrobial retains a constant rate of clinical effectiveness against a specific pathogen, independent of position in the regimen, and that this assumption did not introduce bias in favour of tigecycline. The possibility that factors other than bacterial resistance patterns might influence clinical response has not been considered.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The budget impact assumed 1,010 patients using tigecycline as 2nd line and 101 as 3rd line therapy £685,350 as second line and £68, 530 as third line therapy.

Guidelines and Protocols

In 2005 Scottish Medicines Consortium and the Healthcare associated infection task force issued an Antimicrobial Prescribing Policy and Practice in Scotland that contained Recommendations for Good Antimicrobial Practice in Acute Hospitals.

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.

This assessment is based on data submitted by the applicant company up to and including 18 May 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Babinchak T, Ellis-Grosse E, Dartois N et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clinical Infectious Disease 2005; 41 (suppl 5): S354-67.

Olivia ME, Rekha A, Yellin A et al. A multicentre trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [study ID numbers: 3074A1-301-WW; clinicaltrials.gov identifier: NCT00081744]. BMC Infectious Diseases 2005; 5: 88

Formin P, Beuren M, Gradauskas A et al. Tigecycline is efficacious in the treatment of complicated intra-abdominal infections. International Journal of Surgery 2005; 3: 35-47