17 February 2011
EMA/CHMP/183367/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tygacil

tigecycline

Procedure No.: EMEA/H/C/000644/R/0053

Note

Renewal assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

17 February 2011
EMA/CHMP/183367/2011
Human Medicines Development and Evaluations

CHMP renewal assessment report

Tygacil

(tigecycline)

EMEA/H/C/000644/R/0053

Marketing Authorisation Holder (MAH): Wyeth Europa Ltd

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7<XXX XXXX>
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the renewal

1.1. Marketing authorisation

The European Commission granted the Marketing Authorisation for Tygacil on 24 April 2006 based on a favourable opinion adopted by the CHMP on 23 February 2006.

1.2. Steps taken after the granting of the Marketing Authorisation / last renewal

Changes approved subsequent to the granting of the Marketing Authorisation are listed in Attachment 6.

In addition, the Marketing Authorisation Holder has fulfilled the following follow-up measures/specific as stated in Attachment 7.

1.3. Renewal application

Pursuant to Article 14 (1-3) of Regulation (EC) No. 726/2004, the Marketing Authorisation Holder Wyeth Europa Ltd, submitted to the Agency on 14 October 2010 an application for renewal of the Marketing Authorisation for Tygacil. The expiry date of the Marketing Authorisation is 26 April 2011.

Rapporteur: Gonzalo Calvo Rojas

Co-Rapporteur: Jaana Kallio

Steps taken for the assessment of the renewal:

The Marketing Authorisation Holder submitted an application for renewal of the Marketing Authorisation on:	14 October 2010
The procedure started on:	24 October 2010
The Rapporteur's preliminary assessment report was circulated to all CHMP Members on:	3 January 2011
During the January 2011 CHMP meeting, the CHMP agreed on a List of Outstanding Issues (LoOI) relating to quality and clinical issues that was sent to the MAH on:	20 January 2011
The MAH submitted the responses to the CHMP List of Outstanding Issues on:	26 January 2011
The Rapporteur's updated assessment report on the MAH's responses to the CHMP list of outstanding issues was circulated to all CHMP members on:	6 February 2011
The SAG-AI was convened to address questions raised by the CHMP on:	8 February 2011
The MAH submitted the responses to the further outstanding issues on:	10 February 2011 and 13 February 2011

The CHMP, during its February 2011 plenary meeting, issued a positive Opinion on the renewal of the Marketing Authorisation on:	17 February 2011

2. Scientific discussion

2.1. Introduction

Tygacil (tigecycline) belongs to the glycylcycline class of antimicrobial agents. As a bacteriostatic agent, with a broad spectrum of antibacterial activity, it inhibits the growth of multiple resistant gram-positive, gram-negative, anaerobic, and atypical bacteria, including methicillin-resistant Staphylococcus aureus.

It was authorized in the EU through the centralized procedure on 24 Apr 2006, where it is currently approved for the following indications:

• Complicated skin and soft tissue infections, excluding diabetic foot infections (cSSSI)

• Complicated intra-abdominal infections (cIAI)

A variation application to extend the therapeutic indications to include treatment of community acquired pneumonia (CAP) was withdrawn in the EU in April 2008.

Tygacil is available in single-dose 5-mL glass vials containing 50 mg lyophilized powder for infusion.

2.2. Quality

The Marketing Authorisation Holder has confirmed that the quality, with respect to the method of preparation and control, has been regularly updated by variations to take account of technical and scientific progress in accordance with article 16(1) of Regulation (EC) No 726/2004 and that the product conforms to current CHMP quality guidelines.

It has been confirmed that no changes were made to the product particulars other than those approved by the Competent Authority.

Several quality changes relating to the tigecycline active substance have been introduced since the approval. Most of these changes were minor in nature type I variations (A and B) and concerned manufacturing process, in-process controls and updates of certificates of suitability for the starting material used in the manufacturing process of tigecycline. Furthermore analytical procedures and specification for the drug substance have been modified and the re-test period of the active substance has been extended.

Composition of the finished product was changed and three additional excipients have been added to the reformulated medicinal product, i.e., lactose monohydrate, sodium hydroxide and hydrochloric acid. As a consequence, the manufacturing process has changed, together with the in-process controls and the specifications of the finished product. In addition, minor changes to the container closure system were introduced. Further changes to the manufacturing process of the finished product have been introduced and the in-process controls and parameters for the finished product have been updated to include an in process colour test.

No stability problems have been encountered for the finished product and the shelf-life and storage conditions continue to be fully supported.

Addition compatibility studies have been performed for the product, which resulted in the update of the product information. Sections 6.2 and 6.6 of the SmPC were updated to include information on incompatibility of Tygacil solution with esomeprazole, and solutions for infusion that exhibit a pH above 7 (that can be anticipated for omeprazole solutions for infusion) and compatibility with metoclopramide. The PIL was updated accordingly. Furthermore section 6.6 of the SmPC "Special precautions for disposal and other handling" and section 6 of the PIL "Instructions for use and handling", were updated to include Lactated Ringer's solution for injection as a reconstitution solution and compatible intravenous solution, and to update the information on compatibility for Tygacil diluted in dextrose 50 mg/ml (5 %) solution for injection, when administered through a Y-site.

All the relevant sites of manufacture and testing are undergoing regular GMP inspections by an EEA competent authority or MRA partner authority and satisfactory GMP compliance of these sites has been confirmed by the MAH by submission of the appropriate documentation.

Appropriate declarations have been submitted concerning the GMP compliance status of the active substance manufacturers.

The quality of this product continues to be considered acceptable.

2.3. Non-clinical

The MAH confirmed that no new non-clinical data which would impact the benefit-risk balance are available since the granting of the initial marketing authorisation. No additional publication or non-clinical studies have been submitted with this application

At the time of the MA the MAH agreed to undertake a number of nonclinical follow-up measures (FUMs) concerning results of genetic toxicology studies of relevant human metabolites, degradation products and a T-cell dependent antibody response (TDAR) immune function study; the requested data have been submitted and these FUMs have been considered fulfilled; there are no outstanding non-clinical FUMs.

2.4. Clinical pharmacology

This section discusses clinical pharmacology data that has become available since the marketing authorisation.

2207-WW: Pharmacokinetics of tigecycline in paediatric subjects

Study 2207-WW was a phase 2, multicenter, open-label, ascending multiple-dose study conducted to evaluate tigecycline exposures at dosages of 0.75, 1, and 1.25 mg/kg administered every 12 hours in children aged 8 to 11 years with complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection (cSSSI), or community-acquired pneumonia (CAP). Qualifying subjects received intravenous (IV) tigecycline for a minimum of 3 days to a maximum of 14 consecutive days. The study objective was to identify an appropriate dose regimen of tigecycline for children aged 8 to 11 years old to be tested in phase 3 clinical trials.

Fifty-eight (58) subjects received at least 1 dose of tigecycline and were included in the modified intent-to-treat (mITT) population. A total of 51 of 58 subjects (87.9%) completed the study and 7 (12.1%) discontinued from the study.

Concentrations decreased quickly after the end of the infusion, followed by distribution to a large volume and relatively low clearance. Administration of larger doses resulted in proportional increases in Cmax and AUCτ. Smaller, younger children had lower CL than larger older children; however, no relationship was shown between CLW and weight, body mass index (BMI), or age. No relationship was

shown between CL or CLW and height, sex, or race. No difference in CLW was observed for children with different infections.

The CSR was submitted in April 2010 in accordance to Article 46 of the Paediatric Regulation and is currently under assessment. The evaluation is still on going as additional data related to PK and safety has been requested. In addition the MAH has been requested to submit a type II variation to update section 5.2 of the SmPC with information on PK in the paediatric population.

119-US: Pharmacokinetics of tigecycline in human bone

Study 119 was an open-label, nonrandomized study of multiple doses of tigecycline administered to healthy subjects who were scheduled to undergo a planned bone/joint surgery or procedure. Each subject received 3 IV doses of tigecycline as 30-minute infusions; dose 1 was 100 mg, dose 2 was 50 mg, and dose 3 was 50 mg. Thirty-three healthy men and non-lactating and non-pregnant women, aged 18 years or older, were enrolled in the study, received at least 1 dose of tigecycline, and comprised the safety population. All 33 subjects completed the study.

The serum PK results observed in this study were consistent with what has been reported for other healthy volunteers at steady-state. Tigecycline penetrates into bone, with bone to serum ratios greater than 1 observed at all measured time points following dose 3. The average bone concentration of tigecycline was 898 ng/g, and the ratio of bone and serum AUC0-τ values was 4.77.

The CHMP antibacterial guideline states "Since there are methodological and interpretation problems associated with assays in whole tissues (e.g. homogenates) such studies are not generally helpful; however, drug concentrations at special sites (e.g. concentrations in the CSF) are useful and distribution studies in some other tissue fluids may be valuable". Overall the above study shows that tigecycline is distributed to bone. However the clinical study of tigecycline in patients with diabetic foot infections (DFI) with or without osteomyelitis was negative; this information was included in the SmPC in April 2010 following submission of the study results.

2.5. Clinical efficacy and safety

2.5.1. Clinical efficacy

Since Tygacil marketing authorisation, the MAH completed 1 Phase 3 study in complicated intra-abdominal infections and 3 postmarketing studies in the approved indications.

316-CN: Phase 3 study in Complicated Intra-Abdominal Infections in chinese patients

Study 316-CN was a phase 3, multicenter, randomized, open-label comparison study conducted in China. The primary objective was to compare the safety and efficacy of tigecycline to imipenem/cilastatin in the treatment of Chinese patients with cIAI. Secondary objectives included obtaining in vitro susceptibility data on tigecycline for a range of bacteria that cause cIAI and to compare microbiologic efficacy of tigecycline with that of imipenem/cilastatin. Men or women 18 years of age or older with a cIAI were eligible. Tigecycline was administered every 12 hours (an initial IV dose of 100 mg followed by 50 mg every 12 hours). Imipenem/cilastatin was administered every 6 hours.

The primary endpoint of the study was the clinical response at the test-of-cure (TOC) assessment in the microbiologically evaluable (ME) and microbiologic modified intent-to-treat (m-mITT) populations. Patients were evaluated daily while receiving the test article and again at the post-therapy follow-up visits. Clinical response was determined by the investigator as cure, failure, or indeterminate. Secondary endpoints included microbiologic response at the subject level, microbiologic response at

the pathogen level, for overall and resistant pathogens, clinical cure rates by baseline isolate, response rates for patients with polymicrobial infections and monomicrobial infections, decreased susceptibility, response rates by baseline isolate and MIC values, and susceptibility data by isolate.

The current study was designed to be descriptive and not powered to show non-inferiority versus the active comparator. Therefore, clinical responses were not analyzed for non-inferiority of tigecycline to imipenem/ cilastatin.

Overall, the results showed similar response rates to that observed in the phase 3 pivotal studies. In the ME population, 45 out of 52 (86.5%) tigecycline patients and 47 out of 48 (97.9%) imipenem/cilastatin patients were considered clinical cures at the primary endpoint, the TOC assessment. The clinical cure rates in the m-mITT population for tigecycline and imipenem/cilastatin patients were 81.7% (49 of 60) and 90.9% (50 of 55) respectively. Although it was not powered to test non-inferiority of tigecycline versus imipenem/cilastatin, tigecycline-treated patients had cure rates at the TOC that were lower than those observed for imipenem being the point estimate for the difference in cure proportion in the ME population 11.4% (95% CI -23,5%, 0.7%) in favour of the comparator.

With regards to the microbiologic responses at subject level, eradication rates were similar to clinical cure rates observed. In the ME population, the baseline organisms were eradicated in 45 of 52 (86.5%) tigecycline patients and 47 of 48 (97.9%) patients treated with imipenem/cilastatin at the TOC. The 95% CI for the tigecycline group was (74.2, 94.4); the 95% CI for the imipenem/cilastatin group was (88.9, 99.9). In the m-mITT population, the baseline organisms were eradicated in 49 of 60 (81.7%) patients treated with tigecycline (95% CI, 69.6, 90.5) and 50 of 55 (90.9%) patients treated with imipenem/cilastatin (95% CI, 80.0, 97.0) at the TOC assessment. These differences were less marked.

Among the ME patients with monomicrobial infections, 30 of 33 (90.9% [75.7, 98.1]) patients in the tigecycline group versus 25 of 26 (96.2% [80.4, 99.9]) patients in the imipenem/ cilastatin group were clinically cured at the TOC assessment; however, among ME patients with polymicrobial infections, 15 of 19 (78.9% [95% CI 54.4, 93.9]) patients in the tigecycline group versus 22 of 22 (100% [95% CI 84.6, 100.0]) patients in the imipenem/cilastatin group were clinically cured at the TOC assessment.

Clinical responses at the ME subgroup level, were compared on the basis of the following baseline characteristics: age, sex, ethnicity, clinical diagnosis, and CLCR. In addition, a subgroup analysis of patients with bacteremia was also performed. No unusual findings were observed although the number of patients in each subgroup was too small.

Overall, the limitations of the study are acknowledged since it was not powered to establish non-inferiority. However the study results indicate that, despite the small sample size, there is a trend in favour of the comparator in cIAI, even in situations where patients have relatively low APACHE scores (mean APACHE II score was 4.25 in tigecycline-treated patients and 3.79 in comparator-treated patients, and no patients had APACHE scores ≥15).

315-WW and 400-WW: Phase 4 studies in Complicated Intra-Abdominal Infections

Study 315-WW was a phase 4, randomized, open-label, comparative, multicenter study conducted in Europe, South Africa, the Middle East, and the Asia Pacific region. Study 400-WW was a phase 4,

randomized, open-label, comparative, multicenter study conducted in North and South America. As these studies had a similar design, an integrated analysis of efficacy was performed.

The primary objective was to compare the safety and clinical efficacy of tigecycline to ceftriaxone sodium plus metronidazole for the treatment of hospitalized patients with cIAI. Secondary objectives included comparing the microbiologic efficacy, evaluating in vitro susceptibility data of tigecycline for a range of pathogenic bacteria that cause cIAI, and comparing healthcare use between the treatment groups. Patients were randomly assigned in a 1:1 fashion to receive either tigecycline every 12 hours IV (an initial dose of 100 mg followed by 50 mg every 12 hours) or ceftriaxone sodium 2 g once daily IV plus metronidazole 1 g to 2 g daily in divided doses IV, administered for a minimum of 4 days and up to 14 days.

The primary efficacy variable was the clinical response in the clinically evaluable (CE) population. In both trials, the objective was to show the non-inferiority of tigecycline vs. comparator using a delta of 15% at the test-of-cure (TOC) assessment.

The clinical diagnosis categories considered in these trials were complicated appendicitis, complicated cholecystitis, complicated diverticulitis, intra-abdominal abscess (including liver and spleen), peritonitis (excluding spontaneous bacterial peritonitis), gastric and duodenal perforations, and perforation of the intestines (large, small, traumatic).

The comparator group in both trials was ceftriaxone/metronidazole that was chosen based on its use worldwide for therapy of cIAI. According to the IDSA guidelines, it is a combination regimen commonly used for the treatment of community acquired cIAI of mild to moderate severity. In both studies, most patients had APACHE II scores less than 10 and the overall severity of illness was moderate, therefore the selected comparator is acceptable considering the study objective.

Overall, the design of both trials is in agreement with current guidelines and similar to the phase 3 studies submitted with the marketing authorization application.

Demographic and baseline disease characteristics were similar between the treatment groups in each study. They were also similar between studies except for some differences in weight, BMI and emergency operation. Patients in study 400 had higher weight and BMI that in study 315.

Infection type, etiology of disease, and comorbid conditions were comparable between treatment groups in each study and between studies. The most common clinical diagnosis in both studies was complicated appendicitis (48% in study 315 and 52% in study 400). Therefore, limited data from severe patients are available, similarly to what was observed in the registration trials.

Clinical response

In the integrated analysis of clinical response from both trials, tigecycline met the statistical criterion of non-inferiority, based on a non-inferiority margin of 15%, to ceftriaxone/metronidazole at the TOC assessment (the primary endpoint) and at the EOT assessment in the CE population. In the CE population, at the TOC assessment: 295/387 (76.2%) tigecycline-treated patients and 289/376 (76.9%) ceftriaxone/metronidazole-treated patients were clinically cured. In the CE population, at the EOT assessment: 313/387 (80.9%) tigecycline-treated patients and 315/376 (83.8%) ceftriaxone/metronidazole-treated patients were clinically cured. The lower bound of the 95% CI was -6.8% overall at the TOC assessment and -8.5% overall at the EOT assessment (the adjusted upper bounds were 5.3% and 2.4%, respectively).

The MAH also provided the results of clinical response for the ME population and microbiological response at the subject and pathogen level (ME and m-mITT) as secondary efficacy variables. In addition, the MAH performed secondary analyses for these two variables (e.g. clinical and microbiological responses for monomicrobial vs. polymicrobial infections, clinical response by baseline

isolate and by MIC values). Exploratory analyses of other factors that could affect the clinical response to tigecycline and the differences between treatment groups were also provided. These subgroups considered baseline characteristics such as APACHE II score, age, sex, ethnicity, geographic region, clinical diagnosis, ClCr, prior antibiotic failure status, and concomitant bacteremia.

When individual study information was obtained from the Clinical Study Reports, differences were seen between both trials in the clinical response for almost all the efficacy variables; however, no comparison between results obtained in each study was made by the MAH. For the primary efficacy analysis, the overall difference in clinical response between treatments and for each study is shown in the table below:

	DIFFERENCE (TIGECYCLINE- CEFTRIAXONE/METRONIDAZOLE) Clinical Response (rate of success)* p-value % (95% CI)	
	Study 315	**Study 400**
In CE population	2.4 (-5.6, 10.5) p=0.000	-4.0 (-13.1, 5.1) p=0.009
In ME population	1.8 (-8.8, 12.5) p=0.001	-3.4 (14.5, 7.8) p=0.020

** Negative differences are indicative of better response in the comparator arm.*

In both studies the criterion for non-inferiority was met as the lower bound of the 95% CI for the difference between groups was within the predefined non-inferiority margin of -15%. However, the clinical responses observed in study 400 were lower than those observed in study 315 to the extent that in study 315 the clinical response rate difference was in favour of tigecycline and in study 400 was in favour of ceftriaxone/metronidazole. Only study 315 reached the non-inferiority margin of -10% recommended in the CHMP Guideline on the evaluation on antibacterials.

It was observed that a possible predictor for failure was the APACHE II score. Comparing the clinical response rates by APACHE II score strata in each study for tigecycline and ceftriaxone/metronidazole, response rates were lower for both treatments in study 400 than in study 315, although these differences are more pronounced for tigecycline than for ceftriaxone/metronidazole.

The MAH performed several exploratory sensitivity analyses of clinical response by clinical diagnosis. In principle, the results seem to be consistent with the main analysis, though they should be interpreted with caution due to limited size of some strata.

Microbiological response

In study 315 the percentage of eradications at TOC in the ME population was 82.4% in the tigecycline group vs. 79.8 % in ceftriaxone/metronidazole group, 95% CI for the unadjusted difference: -7.9, 13.3. In study 400, the percentage of eradication at TOC in the ME population was 63.8% in the tigecycline group vs. 70.0% in the ceftriaxone/metronidazole group (95% CI for the unadjusted difference:-13.9, 8.1.).

In regards to the microbiologic responses at subject level, there were differences in the proportion of patients with monomicrobial and polimicrobial infection in each study, i.e in the m-mITT population, for study 315, around 54% of infections were polymicrobial, while in study 400 around 80% of infections were polymicrobial. Overall the percentage of patients with mono and polymicrobial infections that eradicated them in study 315 was higher than in study 400 in the tigecycline group (m-mITT population). This difference is in particular greater for monomicrobial infections, where the clinical success in the m-mITT population for each study were 84.1% in study 315 and 56.3% in study 400. In

polymicrobial infections the responses rates for tigecycline in study 315 and 400 were 72.3% and 63.4% respectively. Responses rates for ceftriaxone/metronidazole were comparable between both studies. Of note, the percentage of superinfection was slightly higher in the tigecycline group than in comparator.

In summary in terms of clinical response, non-inferiority of tigecycline vs. comparator was shown for the two studies. Results on microbiological response are consistent with the main analysis. However the comparison results of these 2 studies raises some uncertainties. Response rates (in terms of both clinical and microbiological response rates) in study 400 were lower than those obtained in study 315. No comparison between results was conducted and no analysis for clinical failures was performed by the MAH. Therefore neither predictors for failure or explanation for the worst response obtained in study 400 have been identified.

900-WW: Phase 4 study in Complicated Skin and Skin-Structure Infections

Study 900 was a phase 3b/4 global, multicenter, randomized, open-label, comparative study, with the primary objective to compare the safety and efficacy of tigecycline with that of ampicillin-sulbactam or amoxicillin-clavulanate in treating patients with cSSSI. The primary endpoint was the clinical response in the CE population at the TOC visit, which was conducted 10 to 28 days after administration of the last dose of study drug. The secondary objectives of the study were to compare the microbiologic efficacy and to evaluate in vitro susceptibility data of tigecycline for a range of pathogenic bacteria related to cSSSI.

Patients were randomly assigned in a 1:1 ratio to receive either tigecycline administered IV every 12 hours (an initial dose of 100 mg followed by 50 mg every 12 hours), or ampicillin-sulbactam 1.5 g to 3 g IV every 6 hours or amoxicillin-clavulanate 1.2 g IV every 6 to 8 hours was administered. Either vancomycin 1 g IV every 12 hours or teicoplanin IV at a loading dose of 400 mg the first day followed by a maintenance dose of 200 mg daily could be added if infection with MRSA was suspected or confirmed within the first 72 hours of enrolment. Treatment was administered for a minimum of 4 days to a maximum of 14 days.

In the analysis of clinical response, tigecycline met the statistical criterion of non-inferiority, based on a non-inferiority margin of 15%, to comparator therapy in the CE population at the TOC assessment. For the CE population, the lower bound of the CI was -8.7% at the TOC assessment and the adjusted upper bound was 8.6%. A total of 162 of 209 (77.5%) tigecycline-treated patients and 152 of 196 (77.6%) comparator-treated patients were clinically cured (difference 0.0; 95% CI, -8.7, 8.6).

The overall mean effect on the primary endpoint is consistent with the previous two trials in cSSSI. Cure rates between tigecycline and comparator were similar and non inferiority was demonstrated.

2.5.2. Clinical safety

The most relevant clinical safety data reviewed during the renewal is an analysis of mortality data from clinical trials conducted with tigecycline since August 2001, where a higher mortality was observed in Tygacil versus comparator-treated patients. The trials included in this analysis were conducted within a 10-year interval, beyond the reporting period of safety data available since Tygacil MA in 2006. Therefore, and considering the relevance of this analysis for the risk/benefit conclusions, it is discussed in a separate section below.

2.5.2.1. Analysis of mortality data from Phase 3 and 4 clinical trials

The MAH refers in the renewal application to an analysis of mortality data of Phase 3 and 4 trials which showed an increase in mortality in patients in tigecycline versus comparator arms. A detailed

discussion of these results had been submitted by the MAH in February 2010 as FU2 29.1 and was under review at the time of the renewal application. Given their relevance for the benefit/risk reassessment of the product, additional information on these analyses was requested to the MAH and the evaluation of these data was completed within the renewal. All data provided by the MAH on the above mortality analysis are discussed below.

Since August 2001, 14 phase 3 and 4 studies of tigecycline have been conducted in approved and non-approved indications (see below).

Phase 3 and Phase 4 Studies Included in the Mortality Analyses (14 Studies Total)

Infection Type/ Study No.	No. TGC-Treated Subjects	Comparator	No. Compar-Treated Subjects	Design
cSSSI	**834**		**813**	
300-US/CA	292	Vanc/Azt	281	DB, 1:1 rand.
305-WW	274	Vanc/Azt	269	DB, 1:1 rand.
900-WW	268	Amp/Sul or Amox/Clav	263	OL, 1:1 rand.
cIAI	**1382**		**1393**	
301-WW	413	Imipenem	412	DB, 1:1 rand.
306-WW	404	Imipenem	413	DB, 1:1 rand.
316-CN	97	Imipenem	102	OL, 1:1 rand.
315-WW	232	Ceftriax/Metronid	235	OL, 1:1 rand.
400-WW	236	Ceftriax/Metronid	231	OL, 1:1 rand.
CAP	**424**		**422**	
308-WW	208	Levofloxacin	210	DB, 1:1 rand.
313-WW	216	Levofloxacin	212	DB, 1:1 rand.
HAP	**467**		**467**	
311-WW	467	Imipenem	467	DB, 1:1 rand.
Non-VAP	336		345	
VAP	131		122	
DFI	**553**		**508**	
319 WW	553		508	
Non-osteo	477	Ertapenem	467	DB, 1:1 rand.
Osteo Substudy	76	Ertapenem	41	DB, 2:1 rand.
RP	**240**		**43**	
307-WW	128	Vancomycin (MRSA)/ Linezolid (VRE)	43	DB, 3:1 rand.
309-WW	112	None	None	OL, non-comparative

The analyses of mortality, including mortality by infection type and overall pooled risk difference, were performed on the 13 studies which had a comparator (thus study 309 was excluded) and wers conducted over a period of time, with differences in the availability of patient level data and time points. Results showed a statistically significant 1% overall risk difference in all-cause mortality between Tygacil and comparator arms.

The analyses considered several patient factors at baseline, but not all variables were available from every study. Factors included age (<65, ≥65 years); sex; race; BMI (<28, ≥28); APACHE II score (≤15, >15, where available); infection type; geographic region (Europe, non-Europe); presence or absence of Acinetobacter spp; P. aeruginosa; history of COPD, CHF, and diabetes mellitus; prior antibiotic failure; albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, creatinine, potassium, and hemoglobin levels; white blood cell

count; and platelet count. In addition, analyses were performed based on "attributable cases" in a subgroup of cases identified by blinded internal reviewers.

The numbers of patients with an adverse event with an outcome of death are summarized by infection type for all 14 studies in the table below. An excess in mortality for the tigecycline-treated patients was observed in 12 of the 13 studies which had a comparator. There were no statistically significant differences observed between treatment groups by infection type.

Patients With Adverse Events With the Outcome of Death by Infection Type for All Phase 3 and 4 Studies (14 Studies Total)

	-Tigecycline -		-Comparator -		Risk Difference*
Infection Type **Study**	**n / N**	**%**	**n / N**	**%**	**% (95% CI)**
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.5, 1.9)
300	5/292	1.7	1/281	0.4	1.4 (-0.8, 3.8)
305	1/274	0.4	0/269	0	0.4 (-1.4, 2.3)
900	6/268	2.2	5/263	1.9	0.3 (-2.7, 3.4)
cIAI	40/1382	2.9	27/1393	1.9	1.0 (-0.3, 2.2)
301	17/413	4.1	12/412	2.9	1.2 (-1.6, 4.1)
306	7/404	1.7	5/413	1.2	0.5 (-1.5, 2.6)
316	1/97	1.0	0/102	0	1.0 (-3.6, 6.4)
315	11/232	4.7	7/235	3.0	1.8 (-2.2, 5.9)
400	4/236	1.7	3/231	0.9	0.4 (-2.6, 4.8)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.3, 2.7)
308	5/208	2.4	6/210	2.9	-0.5 (-4.3, 3.4)
313	7/216	3.2	5/212	2.4	0.9 (-2.9, 4.8)
HAP					
311	65/467	13.9	56/467	12.0	1.9 (-2.6, 6.4)
Non-VAP[a]	40/336	11.9	42/345	12.2	-0.3 (-5.4, 4.9)
VAP[a]	25/131	19.1	14/122	11.5	7.6 (-2.0, 16.9)
DFI					
319	7/553	1.3	3/508	0.6	0.7 (-0.8, 2.2)
Non-osteo[b]	6/477	1.3	2/467	0.4	0.8 (-0.7, 2.5)
Osteo substudy[b]	1/76	1.3	1/41	2.4	NA
RP					
307	11/128	8.6	2/43	4.7	3.9 (-9.1, 11.6)
309	19/112	17.0	NA	NA	NA

Abbreviations: CAP=community-acquired pneumonia; cIAI=complicated intra-abdominal infections; cSSSI=complicated skin and skin structure infections; DFI=diabetic foot infections; HAP=hospital-acquired pneumonia; osteo=osteomyelitis; NA=not available; RP=resistant pathogens; VAP=ventilator-associated pneumonia.

* The difference between the percentage of patients who died in tigecycline and comparator treatment groups.

a. These are subgroups of the HAP population.

b. The primary study of the DFI trial consisted of non-osteo patients and a substudy of the DFI trial was conducted for osteo patients.

Note: The phase 3 and 4 studies include 300, 305, and 900 (cSSSI); 301, 306, 316, 315, and 400 (cIAI); 308 and 313 (CAP), 311 (HAP), 319 (DFI); 307 and 309 (RP).

The 13 phase 3 and phase 4 studies that included a comparator (study 309 was excluded) were pooled in order to estimate the risk difference for AEs with an outcome of death. The absolute risk difference for all-cause mortality was 1.0% (95% CI 0.2, 1.8) between tigecycline- and comparator-treated patients, with 3.9% (147/3788) of patients receiving tigecycline and 2.9% (105/3646) of patients receiving comparator drugs having AEs with an outcome of death.

The analyses did not identify any cause for the increase in all-cause mortality noted in the tigecycline studies. The MAH concluded that deaths were the result of worsening or complications of infection or underlying co-morbidities.

Whilst the magnitude of the risk difference varied across the different infection types, a difference was observed for most of the randomized studies between tigecycline and comparator. In the analysis

presented by the MAH, the hospital-acquired pneumonia (HAP) and resistant pathogens (RP) indications represented the higher mortality risk: 1.9% (95% CI: -2.6, 6.4) and 3.9% (95% CI: -9.1, 11.6), respectively. A greater risk difference was observed in patients with ventilator-associated pneumonia, a subgroup of HAP patients. In the case of EU authorized indications, mortality risks were: 0.7% (95% CI: -0.5, 1.9) for complicated skin and soft tissue infections (cSSSI) and 1.0% (95% CI: -0.3, 2.2) for complicated intra-abdominal infections (cIAI), similar to the overall risk obtained from the overall pooled analysis. Nevertheless, when relative risk measures were calculated (see below), mortality risks of tigecycline in these authorized indications (RR_{cSSSI} = 1.9; RR_{cIAI} =1.5) were similar or higher than those reported in RP (RR_{RP}=1.8) or HAP (RR_{HAP}=1.2). Relative risks are shown in the table below; note that these data were not provided by the MAH.

Relative risks for mortality by infection type in all controlled trials

Indication (s)	Tigecycline n/N	Comparator n/N	N	Relative risk	95%CI		Weights (%)*
RP	11/128	2/43	171	1.8	0.4	8.0	2.75
CAP	12/424	11/422	846	1.1	0.5	2.4	9.09
HAP	65/467	56/467	934	1.2	0.8	1.6	53.23
DFI	7/553	3/508	1061	2.1	0.6	8.2	3.26
cSSSI	12/834	6/813	1647	1.9	0.7	5.2	6.23
cIAI	40/1382	27/1393	2775	1.5	0.9	2.4	25.44
Overall	147/3788	105/3646	7434	1.3	1.0	1.7	100.00

Dersimonian and Laird's heterogeneity test; Q statistic (Chi-square) = 2,359; p-value =0,7975

*Random effects model

Furthermore, when only clinical trial data on tigecycline EU authorized indications were considered, the pooled-relative risk was 1.60 (95% CI: 1.02, 2.42) and pooled-risk difference was 1.0% (95% CI: 0.01, 0.2). No heterogeneity was identified during the evaluation (Q statistic= 0,24; p-value=0,631); (data not provided by the MAH).

A sensitivity analysis was conducted to investigate heterogeneity among studies and infection types. It is noted that the usual way of assessing heterogeneity in meta-analysis is by means of statistical tests such as Cochran's Q and I2 index. However no data were provided by the MAH in this regard. Instead the MAH used a "sensitivity analysis" approach, where the impact of removing each of the studies was evaluated on the combined results, and which may also provide valid information. The analysis showed that the overall mortality increase was not driven by a particular study. The results of the sensitivity analyses performed by the MAH support the robustness of the mortality risk difference.

The analysis by pathogen showed that in both treatment groups, the increase in mortality (percentage of patients) was associated with isolates of *A. calcoaceticus/baumannii*, *E. coli, K. pneumoniae*, *P.aeruginosa*, and MRSA. Of the patients who died, a higher percent in the tigecycline arm had *K. pneumoniae* isolates (16.7% versus 10.3%, tigecycline and comparator, respectively).

Other analyses were performed to determine whether the increase in mortality was related to severity of underlying disease as assessed by APACHE II score. APACHE score was available for the cIAI, HAP,

and RP studies. While the frequency of patients who had AEs with an outcome of death was higher in patients with the higher APACHE scores in each treatment arm, as would be expected, there were no statistically significant differences between the 2 treatment arms for patients with APACHE II scores >15. For patients with APACHE scores ≤15, the differences between treatment groups were statistically significant, consistent with the overall results.

Analyses on AE focused on the initial 10 phase 3 trials, since data from the DFI study (319) and the 3 post-marketing studies (315, 400 and 900) were not available at the time these analyses were performed. The most common AEs with an outcome of death were for tigecycline-treated and comparator-treated patients, respectively: shock (0.8% versus 0.2%), septic shock (0.7% versus 0.3%), pneumonia (0.6% versus 0.2%), heart arrest (0.6% versus 0.2%), and respiratory failure (0.6% versus 0.7%). The differences for shock, heart arrest, and pneumonia were statistically significant.

The table below shows the increase observed in tigecycline-treated patients for events of heart arrest and shock (including septic shock) with an outcome of death.

Number (%) of Patients With Adverse Events of Shock and Heart Arrest with an Outcome of Death for the Initial Phase 3 Studies (10 Studies Total)

	---------Integrated Studies----------		Fisher
	Tigecycline	Comparator	Exact
Adverse event	(n=2611)	(n=2409)	p-Value
Shock and heart arrest	53 (2.0)	18 (0.7)	<0.001*

* Significant between-group difference at the 0.05 level.

Since some of the clinical findings could be indication-related, additional safety data from relevant studies in the approved indications was requested by the CHMP.

For **cSSSI** the MAH submitted a table of serious adverse events (SAEs) from pooled data from the pivotal phase 3 studies (300, 305) and the phase 4 study (900). The incidence of SAEs (overall) was similar between tigecycline and the comparators. However for the 3 studies, an increase was observed for the events of heart arrest and shock including septic shock (10 SAE for tigecycline and 2 for comparators (see table below), and for infections (11 for tigecycline and 4 in comparator).

Number (%) of Patients With AEs of Sepsis, Septic Shock, Shock, and Heart Arrest (TEAEs, SAEs, Discontinuation of Treatment and Deaths,) in the cSSSI Studies

Adverse Event	Overall P-value	Treatment: Tigecycline n=834	Treatment: Comparator n=813
Sepsis			
TEAE through TOC	0.726	5 (0.6)	3 (0.4)
SAE	1.000	2 (0.2)	1 (0.1)
Discontinued Treatment	0.244	0	2 (0.2)
Death	0.000	0	0
Septic Shock			
TEAE through TOC	1.000	2 (0.2)	1 (0.1)
SAE	0.250	3 (0.4)	0
Discontinued Treatment	0.000	0	0
Death	1.000	1 (0.1)	0
Shock			
TEAE through TOC	0.500	2 (0.2)	0
SAE	0.500	2 (0.2)	0
Discontinued Treatment	0.000	0	0
Death	0.500	2 (0.2)	0
Heart Arrest			
TEAE through TOC	0.500	2 (0.2)	0
SAE	0.452	5 (0.6)	2 (0.2)
Discontinued Treatment	0.000	0	0
Death	0.452	5 (0.6)	2 (0.2)

Abbreviations: AE=adverse event; cSSSI=complicated skin and skin structure infections; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TOC=test-of-cure.

Studies 300, 305, 900 (skin). Overall P-value: Refers to No. of Subjects data. Fisher Exact Test P-value (2-Tail). Statistical significance at the .05, .01, and .001 levels is denoted by *, **, and ***, respectively.

Sources: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3074A1 GAR-936/GMA_ISS/Risk Benefit/INTEXT/ AE5-T_TOC-PROT- 09SEP10 10:41, AE5-S-PROT - 09SEP10 10:41, AE5-D-PROT - 09SEP10 10:41, AE5-DEATH-PROT - 09SEP10 10:41

A higher number of deaths due to septic shock, shock and heart arrest in tigecycline-treated patients was also observed in the Phase 4 study 900; this is in line with the above mentioned higher mortality trend observed in the overall analysis in cSSTI patients.

For **cIAI**, the data provided (presented as pooled data from studies 301, 306, 315, 316 and 400), showed that SAEs with outcome of deaths were numerically higher in tigecycline than in comparator (40 and 27 respectively), with an excess risk of around 50%. The number of patients with sepsis, septic shock, shock and heart arrest was 24 in the tigecycline treated patients (which had any of these SAE with an outcome of death) compared with 10 in the comparator treated patients. Any of these events was considered as drug-related. Narratives of deaths submitted by the MAH concluded that they could be explained by the evolution of the disease. However it can be argued that even if they were related to the evolution of the disease, this could imply a lack of efficacy in these patients.

In January 2010, the CHMP agreed that a number of outstanding issues needed to be addressed by the MAH, including a discussion on the possible causes of these findings and key factors which might identify patients at risk of not responding to Tygacil. In response to this request, the MAH provided a combined analysis of the phase 3 and 4 trials by indication (i.e., cSSSI and cIAI) aimed to identify risk factors associated with treatment failure. These analyses comprised mainly: 1) stepwise logistic regression models and 2) non-parametric modelling by means "classification and regression trees (CARTs)". The MAH could not indentify risk factors associated with failure that differentiated tigecycline patients from patients in the comparator group.

In cIAI, pneumonia was identified by the MAH as a confounding factor which could have influenced the increased number of specific adverse events occurred in tigecycline-treated patients. 2.1% of tigecycline-treated patients and 1.2% of comparator-treated patients developed a TEAE of pneumonia. Tigecycline-treated patients who developed pneumonia had a higher incidence of serious events, discontinuation, and death. According to the definition of superinfection applied in clinical trials by the MAH, emergence of a new isolate associated with a clinical event during therapy at a site other than the initial site of infection was considered to be an adverse event. However new isolates emerging at a site other than the initial site of infection (i.e pneumonia) can also be considered as superinfection and therefore cases of pneumonia observed could be interpreted as superinfection. Development of superinfection may therefore have been a relevant contributing factor to the higher risk observed in these patients.

In the CHMP view the analyses provided by the MAH do not exclude a treatment effect. They were performed retrospectively and had relevant methodological and statistical limitations, i.e. comprehensive information on the methodology applied was not presented. Furthermore, as explained above, the trend to higher mortality in tigecycline-treated patients has been consistently observed across studies and type of infections. Whilst the causes of these results have not been identified, this trend cannot be explained by a repeatedly inefficient randomisation leading to an uneven distribution of key prognostic factors between treatment arms in favour of the comparator during the entire clinical development.

In order to further explore a possible explanation to these findings a meeting was held on February 8th 2010 with the Anti-Infectives Scientific Advisory Group (SAG-AI). The experts were asked to address the questions on whether the higher mortality risk in tygecycline-treated patients might be due to insufficient efficacy (dosing, antimicrobial spectrum) in particular clinical situations or to safety issues, and to further discuss whether key factors determining insufficient response in cSSTI and cIAI could be identified.

The experts acknowledged the small but consistent trend towards an increase in mortality observed throughout the different trials of tigecycline development programme, and concluded that there was insufficient data to reach conclusions on the main determinants of these findings. They agreed that in relation to the licensed indications, this phenomenon appears to be associated with differing causes of death such as late, non-infectious complications, or occurrence of pneumonia. They also advised that the product information be strengthened to ensure adequate use and minimise the risks in severely ill patients; this should include appropriate warnings on superinfections.

2.5.2.2. Cumulative experience from 15 Jun 2005 through 15 Aug 2010

The MAH has included in the discussion for this section a first PSUR covering the period 15 June 2005 to 14 December 2005, which was not submitted in the EU since Tygacil was not yet authorised. The first PSUR submitted in the EU covered the period 15 December 2005 to 14 June 2006. The cumulative number of patient exposed to tigecycline since 15 December 2005 through 15 Aug 2010 is estimated to be 944,831 patients.

Since the MA, 5 6-monthly PSURs and two annual PSURs have been submitted. A bridging summary review covering the period from 15 June 2005 to 15 August 2010, which includes information from the PSURs previously submitted, has been included in the renewal application.

In the tigecycline PSURs, the following topics were presented (those topics that are included in the risk management plan and therefore subject to a close monitoring are designated with an asterisk (*)): nausea and vomiting, diarrhea including *Clostridium difficile*-associated diarrhea and pseudomembranous colitis*; hypersensitivity reactions including anaphylaxis*; prolonged PT and

aPTT; renal disorders, including increased BUN; hepatic disorders* including hyperbilirubinemia/severe jaundice, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) abnormalities; pancreatitis*; hypoproteinemia; cardiovascular events, including QTc prolongation/torsade de pointes*; thrombocytopenia*; hearing loss; drug interactions: seizure; skin hyperpigmentation; dermatologic reactions. Relevant events are discussed below:

Pancreatitis

In the most recent PSUR, a cumulative review of reports of tigecycline-associated pancreatitis was presented. Out of the 108 reports reviewed 105 cases were considered serious. The review did not provide relevant new information. As reflected in the risk management plan (RMP), the MAH has been requested to use a specific questionnaire for the reported cases.

Hepatobiliary disorders

In the most recent PSUR, and with data lock point June 2009, and following a CHMP request, the MAH provided a cumulative review of tigecycline-associated hepatic failure and severe hepatic injury hepatic cases. A total of 24 cases of hepatic failure/encephalopathy/hepatorenal syndrome were reported. Outcome was provided in 21 cases; of them, 19 had a fatal outcome (90%). In seven cases hepatic failure occurred in the setting of multiorgan failure and sepsis. The evaluation of these cases did not allow drawing definitive conclusions.

Hypersensitivity Reactions

A total of 7 reports of Stevens-Johnson syndrome (SJS) have been received cumulatively. As requested by the CHMP following the assessment of the last PSUR, the MAH is including SJS to the list of adverse reactions in the SmPC.

Fatal cases

Cases in which the death is caused or related to a progression and/or complication of the infectious disease treated with tigecycline represented about 50% of fatal reported cases where causality could be assessed.

Lack of efficacy

Efficacy related case reports have been reported and analysed in all PSURs presented to date; the MAH has identified 18, 40, and 19 reports of tigecycline lack of efficacy in PSUR-7, PSUR-6 and PSUR 5, respectively. This represents 10-15% of all individual safety case reports received during these periods. The sources of some cases are reports published in the medical literature:

- Anthony k et al. "Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. Clin Infect Dis 2008; 46:567–70". According to the authors, the experience of 18 patients who received tigecycline as treatment for infection due to multidrug-resistant gram-negative bacilli, observed evolution of resistance during therapy, which raises concerns on the routine use of tigecycline in treatment of such infections when other therapies are available.
- García- Cabrera et al. "Superinfection during treatment of nosocomial infections with tigecycline. Eur J Clin. Microbiol Infect Dis (2010)29:867-871" have evaluated the occurrence of superinfection (defined as the isolation of bacterial strains different to those causing the primary infection) during tigecycline treatment. In this study the superinfection rate during tigecycline treatment was 23.5% being P. aeruginosa the most frequent pathogen, responsible for 58.3% of superinfections. Considering the potential risk of infection with P.aeruginosa and other resistant bacteria, the authors have suggested a tight surveillance in the follow up of patients treated with tigecycline.

Off label use

In the last PSUR (15 June 2009 to 14 June 2010) the MAH presented the results of a European utilization study. Following a CHMP request to provide a more detailed evaluation of the results, including an analysis of numbers and characteristics of patients treated for off-label indications and a discussion of factors modifying the level of this off-label use, additional information was submitted on February 2011. Based on this study, 23,714 patients hospitalized in 2008 were treated with tigecycline. The proportions of on-label and off-label users were 38.7% and 61.4% respectively. This drug utilization study also provided information on distribution of pathogens stratified by indication. In regards to pathogens isolated from patients treated for the EU approved indications in 2007-2008, 938 isolates were obtained from intra-abdominal infection/pelvic abscess patients (IAI) and 6391 from skin/skin structure infections (SSSI) patients. Pseudomona aeruginosa (inherently resistant organism) was found in 64 (6,8%) of IAI and 82 (1,3%) of SSSI isolates, and other organisms for which acquired resistance may be a problem (Acinetobacter sp., Enterobacter aerogenes, Klebsiella neumoniae) were found in 291 (31%) of IAI and 1548 (24%) SSSI isolates. In view of these data, the MAH has been requested to update the RMP in regards to off-label use.

Following assessment of the last PSUR the MAH has been requested to provide the following information:

- a specific questionnaire aimed to gather relevant information from reports of cases of suspected hepatic failure associated to tigecycline treatment.
- a cumulative analysis of reports Stevens-Johnson syndrome, extended also to other severe cutaneous adverse reactions, as toxic epidermal necrolysis.
- A detailed discussion of specific aspects of the results of the European Tygacil drug utilization study submitted with the last PSUR.

The MAH submitted this information in February 2011 and it is currently under assessment. In parallel a variation to include the term *Stevens-Johnson syndrome* in section 4.8 of the SmPC has been submitted.

Changes in the Product Information

Relevant changes made in the SmPC since the MA as a result of new safety data reviewed in the PSURs are listed below:

- Pancreatitis was included in section 4.4 and removed from the tetracycline-class effect.
- Anaphylaxis/anaphylactoid reactions were included in section 4.4 and 4.8. Thrombocytopenia was also included in section 4.8.
- Jaundice and liver injury were added as adverse reactions in Section 4.8.
- Section 4.4 and 4.8 were updated to include reference to cases of significant hepatic dysfunction and hepatic failure.
- Following submission of the 6th PSUR (June 2008-June 2009), the CHMP requested the MAH a review of safety data in severely ill patients and from new phase 4 studies. In april 2010 section 4.8 of the SmPC was amended to update the mortality data from cSSSI and cIAI studies, which was based on 1415 patients; the revised figures were based on an updated study database (including a recently completed phase 3 study in DFI and 3 phase 4 studies) and 2514 patients.

In addition, and following submission of the results of a study in diabetic foot infections, the SmPC was updated to add in section 4.1 that Tygacil is not indicated for diabetic foot infections; section 4.4 was updated with information from this study.

Pharmacovigilance system

Following the acquisition of Wyeth by Pfizer, which was completed on 16 October 2009, the Wyeth pharmacovigilance system (PhVS) was decommissioned and a new Pfizer pharmacovigilance system was implemented effective from 8 November 2010. The introduction of the new PhVS is not expected to have any impact on Tygacil benefit/risk balance. In this respect the MAH has recently submitted in February 2011 an application for a worksharing procedure (WS/0117) for the introduction of a new PhVS (update to the DDPS) for Tygacil and which also applies to other Centrally Authorised Products from the same MAH. This new system and DDPS have been assessed and agreed during the recent review of a MAA, from the same MAH, which received a positive CHMP opinion on 16 January 2011.

2.5.2.3. Report of post marketing experience 15 June 2010 to 15 August 2010. Overall safety evaluation

In addition, the MAH submitted within the renewal dossier an addendum of the most recently submitted PSUR (15 June 2009 to 14 June 2010). This addendum report covers the period from 15 June 2010 to 15 August 2010. During this reporting period a total of 54 medically confirmed case reports from spontaneous (n=40) and study (n=14) notifications were received. Of these 54 reports, 41 contained at least 1 SAE, and 13 were non-serious. Of the 41 SAE reports, 27 were received from spontaneous notifications and 14 were received from the study environment, including 12 reports which originated from a single published case series by Garcia-Cabrera et al.

Fatal case reports

During this reporting period, 9 reports with fatal outcome (4 spontaneous and 5 from study environment) were received. Of the 5 reports originated from an observational study of 51 patients, 3 died due to superinfections and 2 due to underlying diseases. Cases in which the death is caused or related to a progression or complication of the infectious disease treated with tigecycline represented about 50% of fatal reported cases. As in the previous PSUR in a relevant percentage of the cases only limited information was provided by the MAH in relation the cause of death.

Hepatobiliary Disorders

During this reporting period, 6 reports of hepatobiliary disorder were received (5 serious, 1 non-serious). Hepatic failure is expected to be a relevant feature in cases where lack efficacy of the treatments leads to sepsis and multi-organic failure.

Nausea and Vomiting

During this reporting period, 6 reports (5 non-serious, 1 serious) of nausea and vomiting were received Nausea and vomiting are already include as ADR in the EU-SmPC. During the last PSURs, the increase in the number of cases has been considered a possible concern. Serious events of nausea and vomiting should continue to be monitored trough the PSUR.

Pancreatitis

During this reporting period, 7 reports of pancreatitis were received, all of them serious and 70% were recovered following tigecycline withdrawal. Pancreatitis should continue to be monitored through PSUR and RMP.

Hypersensitivity Reactions

During this reporting period, 1 report of hypersensitivity reaction was received. In addition 1 new case of Guillain Barré syndrome has been reported. To date, none reports of Guillain Barré syndrome had been identified. This is a very rare and severe syndrome, which had not been reported previously. The MAH should continue to monitor these events, including Stevens-Johnson and Guillain Barré syndrome, through the PSURs and RMP.

Lack of efficacy

During this reporting period, 3 reports of lack of tigecycline effect were received. In addition while not meeting the criteria for lack of efficacy, 12 reports describing superinfection in patients who received tigecycline for multidrug-resistant nosocomial infections originated from a single published retrospective case series by Garcia-Cabrera et al. above mentioned.

As already mentioned lack of efficacy is a serious concern with Tygacil. In this respect the information in the PSUR addendum report is consistent with previous PSURs. As already mentioned new isolates emerging at a site other than the initial site of infection (i.e cases of pneumonia associated with an outcome of death) during antibacterial treatment should be considered as superinfection. This is in line with the above mentioned published report. Therefore the current general statement in section 4.4 of the SmPC on the rate of superinfection should be strengthened. In addition "development of superinfection" should be included in the RMP as an identified risk to be closely monitored in clinical practice.

Off-label Use

More than 30% of the reports received during the reporting period describe off-label use. Moreover, 44% and 50% of the reports in off- label and on-label use describe lack of tigecycline effect respectively. As discussed in the next section, the MAH will update the RMP in regards to off-label use, and implement risk minimisation measures.

Other adverse reactions and risks which should be monitored through PSUR/RMP are Skin hyperpigmentation, renal disorders, thrombocytopenia, potential for drug interactions, drug overdose and prescription/medication errors.

2.5.2.4. EU Risk Management Plan

The current version of the EU Risk Management Plan (vs 6) was submitted by the MAH in August 2010 As requested in the previous PSUR, severe hepatic reactions was re-classified as an important identified risk. Identified risks included in the plan are *Clostridium difficile*-associated diarrhea and pseudomembranous colitis, hyperbilirubinemia/jaundice, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) abnormalities, severe hepatic reactions, hipersensitivity reactions including anaphylaxis, pancreatitis and thrombocytopenia. These terms are included in the SmPC. Based on reports of Stevens-Johnson syndrome (SJS), it is being included in section 4.8 of the SmPC (see above section). A potential risk included in the plan is QTc prolongation/torsade de pointes.

In the current Risk Management Plan (vs 6), the potential off-label use is discussed and is included in the Safety Specification section. The MAH is requested to update the "Potential for Off-Label Use" section considering the results of the European utilization study which show that at least 60% of the patients in a relevant sample in Europe hospitals are treated for non approved indications.

The higher rates of certain serious adverse events (SAE) and of fatal outcomes consistently observed across Tygacil studies and the risks identified during the evaluation of all available data, including postmarketing experience, warrant the implementation of specific measures in Tygacil risk

management plan. Currently there are no risk minimisation measures in the RMP. The CHMP concluded that the following measures were required to be implemented by the MAH:

- Distribution of a DHCPL addressed to Tygacil prescribers to inform of the mortality findings, and the changes in the product information strengthening that Tygacil should only be used in the approved indications when other suitable alternatives are not available. It will also advise on the need of a close monitoring of patients and switch to alternative antibacterial therapy if superinfection occurs.
- Implementation of an Educational Program addressed to the HCP which will include scientific information on the SmPC changes. The program will focus on the need to further characterize superinfections (both new isolates emerged during therapy at the initial site of infection and a site other than the initial) and lack of efficacy. It will also warn about the off-label use risks.
- Set-up of a prospective Post Authorisation safety Study (PASS) to monitor emergence of superinfections and treatment failures, as relevant risks identified in the RMP. The study will be conducted in a selected number of representative centres of the EU clinical setting and will also provide microbiology data. Information on Tygacil prescription patterns will also be obtained.

The CHMP has recommended that the above measures be a condition of the renewal of the marketing authorisation (see Annex II). The full revised RMP will be submitted by the MAH after the Commission Decision.

2.5.2.5. Conclusion on Safety

As explained above higher mortality rates have been observed in clinical trials among Tygacil versus comparator-treated patients. These findings, though more pronounced in particular clinical situations, are consistent across the development program, and are also seen in recent post marketing trials conducted in the approved indications. Although the causes of the higher mortality risk have not been identified, a lower than expected efficacy of Tygacil cannot be ruled out. Several factors may have contributed to the fatal outcomes, i.e. poor baseline conditions and presence of co-morbidities; emergence of superinfections during treatment is likely to have influenced the overall findings.

The safety of tigecycline has been followed through PSURs and a RMP, which also discuss as relevant issues reports of death and lack of efficacy as well as off-label use. Other findings observed in the clinical trials are also described in these post-marketing reports i.e. development of superinfection.

Currently lack of efficacy is monitored in all Tygacil clinical trials with particular focus on severely ill patients with cIAI and cSSSI (FUM 19). In addition the results of the Tygacil European Surveillance Trial (TEST) study aiming to monitor the emergence of resistance in the EU are provided regularly (FUM 17). The MAH will continue to submit reports on both topics on a yearly basis.

The MAH also committed in the Letter of Undertaking from February 2002 to provide the results of a pharmacokinetic study (307A1-120-US) of tigecycline in patients with biliary cirrhosis. The CSR submission has been postponed as is now due for the end of March 2011.

The CHMP has recommended that measures aimed to secure a safe use of Tygacil and minimise the risk of fatal outcome in susceptible or severely ill patients be implemented by the MAH. These measures include:

- SmPC amendment to indicate that Tygacil should only be used in the approved indications when there are no suitable therapeutic alternatives, and to warn about the mortality findings, the need to closely monitor patients and institute alternative antibacterial therapy if superinfection occurs.

- Implementation of a risk minimisation plan aimed to address the risks of superinfections, lack of efficacy, and off label use and a post-authorisation safety study which will provide relevant data and monitor these risks.

The MAH submitted 5 6-monthly PSURs, 2 annual PSURs plus a 2-month PSUR addendum. The CHMP has recommended that PSUR should continue to be submitted annually. The next PSUR submission is due by August 2011.

The risk minimisation plan and the post-authorisation safety study have been recommended to be a condition of the renewal of the marketing authorisation.

Based on the above conclusions, the CHMP has recommended that the MAH submits one additional renewal application.

2.6. Product information

2.6.1. Summary of product characteristics, labelling and package leaflet

Taking into consideration the higher mortality observed in clinical trials in tigecycline-treated patients, the CHMP considers that Tygacil SmPC needs to be amended to warn HCP of these findings and to make recommendations aimed to minimise the occurrence of fatal outcomes in particular in the most susceptible and severely ill patients. Therefore the CHMP has requested further amendments to the product information during the procedure.

The higher mortality risk in Tygacil-treated patients is acknowledged. Considering all available data a lower efficacy of tigecycline over comparator treatments in patients treated for the authorised indications cannot be excluded. Therefore the CHMP has recommended that a new statement be added to the indication section to restrict Tygacil use in the approved indications cSSSI and cIAI to those situations where other suitable alternatives are not available, aiming to be used only when it is really needed.

The CHMP has also recommended the inclusion of new warnings to inform prescribers of the higher mortality observed in Tygacil trials; in addition the potential role of a lower efficacy of tygecicline in these findings, needs to be specifically stated. As discussed above the development of superinfections, in particular pneumonia, seems to have a relevant influence in the outcome; therefore and in line with the advise provided by the SAG experts, a warning has been added to section 4.4, to recommend closely monitoring of patients, specifically the potential development of infections in focus other than the initial cIAI and cSSSI, and to institute alternative antibacterial treatments if this occurs.

The inclusion of additional warning aiming to address the off-label use has also been warranted. As the drug utilisation study and PSUR data provided by the MAH demonstrate, Tygacil is widely prescribed in non approved indications. Therefore an additional statement has been added to section 4.4 to strengthen that Tygacil should not be used in other indications that those in which it is specifically authorised, namely cSSSI and cIAI.

Taking the above into account, the CHMP has recommended that the following information be included in sections 4.1 and 4.4 of the SmPC (new text in italics).

4.1 Therapeutic indications

Tygacil is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections, excluding diabetic foot infections (see section 4.4)
- Complicated intra-abdominal infections

Tygacil should be used only in situations where it is known or suspected that other alternatives are not suitable (see sections 4.4 and 4.8).

……..

4.4 Special warnings and precautions for use

In clinical studies in complicated skin and soft tissue infections, complicated intra-abdominal infections, diabetic foot infections, nosocomial pneumonia and studies in resistant pathogens, a numerically higher mortality rate among Tygacil treated patients has been observed as compared to the comparator treatment. The causes of these findings remain unknown, but poorer efficacy and safety than the study comparators cannot be ruled out.

Patients who develop super-infections, in particular nosocomial pneumonia, appear to be associated with poorer outcomes. Patients should be closely monitored for the development of super-infection. If a focus of infection other than cSSTI or cIAI is identified after initiation of Tygacil therapy consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Tygacil is not approved for clinical indications other than complicated skin and soft tissue infections, and complicated intra-abdominal infections. The use of Tygacil in non-approved indications is not recommended.

…..

The MAH proposed changes to the Product Information (PI) at the time of the renewal application to bring it in line with the current version of the QRD template (v7.3). According to this, and in line with the SmPC guideline, information on fertility has been included in sections 4.6 and 5.3 of the SmPC. Other minor amendments have been made as per the above guidance. These changes were reviewed by QRD and accepted by the CHMP.

2.6.2. General conditions for the marketing authorisation

Annex II.B – Conditions of the Marketing Authorisation

The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.

The following information has been included in Annex IIB:

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The Marketing Authorisation Holder (MAH) should inform all healthcare professionals who are expected to prescribe/use Tygacil about the new important identified and potential risks of the product by means of a Direct Healthcare Professional Communication (DHPC)

Within 1 month of the Commission Decision the MAH shall ensure that all healthcare professionals who are expected to prescribe/use Tygacil are invited to participate in a specific Educational Program (EP), aimed at communicating scientific information regarding the new changes in the SmPC (i.e. the new identified risk of superinfection, and the new potentials risks of lack of efficacy and off label use. The key elements of the EP should have been previously agreed with the CHMP. Final materials for the EP should be approved by National Competent Authorities according to national regulations.

OTHER CONDITIONS

The MAH shall perform a Post-Authorisation Safety Study (PASS) aimed at describing how Tygacil is prescribed and monitoring superinfections and treatment outcome. For this purpose, the MAH should perform the PASS according to a final protocol agreed with the CHMP. Results will be provided by Q2 2012.

Risk Management Plan

…..

The MAH commits to include the risk minimization activities identified above and the PASS in the Risk Management Plan (RMP). The new RMP should be submitted within 2 weeks of the Commission Decision.

…..

Attachment 7 of this Assessment Report includes the SPC, Annex II, and PL for of Tygacil as a relevant example, where all adopted changes are annotated.

2.7. Follow-up measures to be fulfilled by the MAH

No new follow-up measures have been requested as a result of the renewal procedure. New conditions have been required and are included in Annex II. The outstanding follow-up measures from previous MAH commitments are listed below:

Area1	**Description**	**Due date**
Quality	**FU2 047.2** (resulting from FU2 047.1) From II/14: The MAH will provide data supporting a preliminary specification with information gathered on ten batches of drug product up to 12 months, followed by updated data at the end of the approved shelf-life. Updated limits will be submitted on the basis of the information collected. Data which is to be provided will include: • Colour measurements on diluted solution [admixture] at t=0 (dilution of the reconstituted solution) and at t=60 minutes (maximum potential in-use stability period). ΔE* will be calculated in accordance with USP • A proposal for a preliminary specification for an E* range and ΔE* calculated with reference to colour measurements at t=0, as supported by data generated One set of median values will be used as standard values (L*, a* and b*). The potential for review of these values on an ongoing basis will be evaluated while collating the above data and will be confirmed at the end of the program i.e. at the end of the approved shelf-life	28 Feb 2011
Quality	**FU2 049.4**: The MAH will provide data supporting a preliminary specification for Suitability & Colour tests with information gathered on ten batches of drug product and ten batches of drug substance up to 6 months, followed by updated data at 12 months and the end of the approved shelf-life. Updated limits will be submitted on the basis of the information collected.	End of February 2011

Quality	**FU2 050.3**: The MAH will provide data supporting a preliminary specification for Colour of Solution tests with information gathered on ten batches of drug product and ten batches of drug substance up to 6 months, followed by updated data at 12 months and the end of the approved shelf-life. Updated limits will be submitted on the basis of the information collected.	End of February 2011
Clinical	**FUM 017** (23/02/2002 LOU): The MAH commits to present the results from the Tigecycline European Surveillance Trial (T.E.S.T.) aimed at monitoring emerging resistance in the European Union.	Annually
Clinical	**FUM 019**(23/02/2002 LOU): To monitor the lack of efficacy in all planned or ongoing trials with tigecycline, mainly focusing on severely ill patients with cSSTI and cIAI.	Annually in PSUR
Clinical	**FU2 021.2** (23/02/2002 LOU): The MAH should submit the results of the open-label, single-dose study of the pharmacokinetics of tigecycline in adults with primary biliary cirrhosis (Study 3074A1-120-US)	End of May 2011
Clinical	**FU2 52.2:** The MAH will provide responses to questions raised by the CHMP in Jan 2011 on paediatric study 3074K4-2207-WW submitted in accordance to article 46 (P46-052) concerning the dose selection to be tested in phase 3 trials in paediatric patients and the Pop PK analysis submitted. In addition will submit a variation to update section 5.2 of the SmPC with information on PK in paediatric population	End of March 2011

2.8. Conclusions on benefit risk balance of the product

At the time of the initial MAA a number of issues were identified by the CHMP, among them, the questionable representativeness of the population enrolled in the pivotal studies (in terms of both, severity of infections and co-morbid conditions) and a numerically increased mortality among Tygacil treated patients. Based on all efficacy and safety data submitted, a positive benefit risk conclusion was agreed at the end of the procedure, together with relevant amendments in the product information which highlighted the limitations of the clinical studies and a number of post-marketing commitments aimed to address the concerns identified. The available data was insufficient to recommend additional warnings or restrictions.

A number of post-marketing studies in approved (cSSSI and cIAI) and non-approved indications (HAP, DFI and resistant pathogens) have reproduced the higher mortality trend observed with Tygacil, thus confirming the initial findings. As expected, differences are small, but consistently present. This prompted the submission by the MAH of a review of the mortality analyses prior to the renewal application. Given the relevance of these safety findings for the product benefit/risk reassessment, and following preliminary discussions held by the CHMP in December 2010, the evaluation of these data was completed within the renewal procedure.

As stated above, clinical trials in all indications have shown a small but consistent trend towards a higher risk of death among patients treated with Tygacil than that observed in comparator-treated patients. In many circumstances, and this is not an exception, it is difficult to determine whether the main factor contributing to an increase in mortality is that the product lacks the expected efficacy or it is linked to a toxicity issue. In the case of Tygacil no definitive answer can be given with certainty. However, the fact that deaths are frequently associated to clinical events like shock, sepsis and heart

arrest, seems to indicate that an inadequate response to the product may be behind a relevant number of cases with fatal outcome.

In an attempt to identify risk factors associated to the fatal outcomes, the MAH has provided a number of analyses that are acknowledged though are of questionable validity to truly establish their real causes. There is not probably a single contributing factor. Aspects such as advanced age, severity of the disease, clinical status of the patient, co-morbid conditions, altered immunocompetence, etc, not strictly related to the treatment, are likely to play a relevant role. However, when within a series of randomised clinical trials in different indications, conducted in different geographical areas and at different points in time, the same finding is consistently observed, it has to be inferred that treatment is to some extent responsible for it. In the CHMP view, and taking into account all available information, this possibility cannot be excluded and needs to be seriously considered.

It is difficult to determine the factors associated with Tygacil therapeutic failures; it is likely that a combination of factors, rather than a single one, is responsible for them. The selection of certain pathogens, superinfections with non-susceptible pathogens, relative underdosing in very obese and morbidly obese patients, may be contributing (isolated or jointly) to treatment failure and, ultimately, patients death. Unfortunately, in the CHMP view, new analyses of existing data will be of limited help to provide further insight into this issue, which can only be prospectively addressed in future studies and surveillance programs.

Off label use is not a unique feature of Tygacil, but is a common practice with antibiotics in clinical situations where therapeutic decisions are guided by microbiological data and local pattern of resistance. However, the fact that more than half of the drug prescriptions of Tygacil are off label further complicates the approach to the problem.

The increase of antimicrobial resistance is limiting the treatment options available. In this respect the CHMP acknowledges the need for antibiotics, particularly those directed against multiresistant Gram-negative bacteria, such as tigecycline. In this respect Tygacil may certainly provide added value to patients in specific clinical situations. However given the higher mortality risk observed in patients treated with tigecycline, the CHMP has recommended that Tygacil use in the approved indications cSSSI and cIAI be restricted to those situations where other suitable alternatives are not available, aiming to limit its use to those cases where it is really needed.

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Tygacil remains positive, but considers that its safety and efficacy profile is to be closely monitored for the following reasons:

- In an analysis of clinical studies a higher mortality rate was observed in Tygacil versus comparator-treated patients. This trend has been consistently observed throughout the product clinical program, and has been maintained in recent post marketing trials in the approved indications.
- The causes of these findings have not been identified but a lower than expected efficacy of Tygacil cannot be ruled out.

The CHMP has recommended that measures aimed to secure a safe use of Tygacil and minimise the risk of fatal outcome in susceptible or severely ill patients be implemented by the MAH. These measures include:

- SmPC amendment to indicate that Tygacil should only be used in the approved indications when there are no suitable therapeutic alternatives, and to warn about the mortality findings, the need to closely monitor patients and institute alternative antibacterial therapy if superinfection occurs.

- Implementation of a risk minimisation plan aimed to address the risks of superinfections, lack of efficacy, and off label use and a post-authorisation safety study which will provide relevant data and monitor these risks.

In view of new data reviewed as part of the renewal application, the CHMP recommends amendments to the Annexes I, II and IIIB. These changes do not affect the benefit/risk balance of the product which remains positive.

The CHMP is of the opinion that one additional five-year renewal on the basis of safety grounds is required.

3. Outcome of the renewal

Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Tygacil continues to be favourable.

The CHMP recommends the renewal of the Marketing Authorisation for Tygacil, subject to the conditions as laid down in Annex II to the Opinion as well as the outstanding commitments of the Marketing Authorisation Holder as laid down in his Letter of Undertaking (see Attachment 9) of this Assessment Report.

The CHMP is however of the opinion that one additional five-year renewal on the basis of safety grounds is required. The grounds for one additional renewal are set out in the Annex IV to the opinion.

The renewal requires amendments to the terms of the Community Marketing Authorisation. The following annexes have been amended: I, II and IIIB.

4. EPAR changes

The EPAR will be updated following Commission Decision for this renewal application. In particular the EPAR steps after the authorisation" will be updated as follows:

Scope:

Renewal of the Marketing Authorisation

Summary:

In an analysis of clinical studies a higher mortality rate has been observed in Tygacil versus comparator-treated patients. The higher mortality trend has been consistently observed throughout the product clinical program, and has been maintained in recent post-marketing trials in the approved indications. The causes of these findings have not been identified but a lower than expected efficacy of Tygacil cannot be ruled out.

The CHMP has recommended that measures aimed to secure a safe use of Tygacil and minimise the risk of fatal outcome in susceptible or severely ill patients be implemented by the MAH. These measures include:

- SmPC amendment to indicate that Tygacil should only be used in the approved indications when there are no suitable therapeutic alternatives, and to warn about the mortality findings, the need to closely monitor patients and institute alternative antibacterial therapy if superinfection occurs.
- Implementation of a risk minimisation plan to address the identified risks, in particular superinfections, treatment failures and off-label use, and a post-authorisation safety study expected to provide relevant data and monitor these risks.

The CHMP is of the opinion that one additional five-year renewal on the basis of safety grounds is required.