HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 November 2011

TYGACIL 50 mg, powder for solution for infusion
B/10 glass vials of 50 mg (CIP code: 567 032-0)

Applicant: PFIZER

Tigecycline
ATC code: J01 AA12 (antibiotic belonging to a subgroup of the tetracyclines: the glycylcyclines)

List I
Medicinal product reserved for hospital use

Date of Marketing Authorisation: 24 April 2006, correction of MA on 6 May 2011 (modification to the therapeutic indication)
European MA by the centralised procedure

Reason for request: Re-assessment of the actual benefit in accordance with article R.163-21 of the Social Security Code. This re-assessment follows a pharmacovigilance alert relating to an increased mortality observed in the course of clinical studies carried out both in indications validated and not validated by the Marketing Authorisation (MA).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tigecycline

1.2. Indications (changes to the SPC in bold: correction of 6 May 2011)

"TYGACIL is indicated in adults for the treatment of the following infections:

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections.

TYGACIL must not be used except in the absence of an appropriate alternative treatment.

Consideration should be given to the official recommendations on the appropriate use of antibacterial agents."

1.3. Dosage

Dosage

The recommended dose for adults is an initial dose of 100 mg followed by 50 mg every 12 hours for 5 to 14 days.
The duration of therapy should be guided by the severity, site of infection, and the patient's clinical response.

Hepatic insufficiency

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B).
In patients with severe hepatic impairment (Child Pugh C), the dose of TYGACIL should be reduced to 25 mg every 12 hours following the 100 mg loading dose. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see sections 4.4 and 5.2 of the SPC).

Renal insufficiency

No dosage adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis (see section 5.2 of the SPC).

Elderly patients

No dosage adjustment is necessary in elderly patients (see section 5.2 of the SPC).

Paediatric population

The tolerance and efficacy of TYGACIL in children below 18 years have not yet been established. No data are available (see sections 5.2 and 4.4 of the SPC).

Method of administration

TYGACIL is administered only by intravenous infusion over 30 to 60 minutes (see section 6.6 of the SPC).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6 of the SPC.

1.4. 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 infections due to resistant pathogens, a higher mortality rate among patients treated with TYGACIL has been observed compared with those on the comparator treatment.
The causes of these findings remain unknown, but poorer efficacy than the 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 a complicated skin and soft tissue infection or a complicated intra-abdominal infection is identified after initiation of TYGACIL therapy, consideration should be given the use of an alternative antibiotic therapy that has been demonstrated to be efficacious in the treatment of this new infection.
TYGACIL is only indicated for the treatment of complicated skin and soft tissue infections or complicated intra-abdominal infections in adults. The use of Tygacil in non-approved indications is not recommended.

Anaphylaxis/anaphylactoid reactions, potentially life-threatening, have been reported with tigecycline (see sections 4.3 and 4.8).

Cases of liver injury with a predominantly cholestatic pattern have been reported in patients receiving tigecycline treatment, including some cases of hepatic failure with fatal outcome. Although hepatic failure may occur in patients treated with tigecycline due to the underlying condition or concomitant medical products, a possible contribution of tigecycline should be considered (see section 4.8).

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline may have adverse effects similar to those of tetracycline class antibiotics. Such effects may include photosensitivity, pseudotumor cerebri, pancreatitis, an anti-anabolic action which has lead to increased BUN, azotaemia, acidosis and hyperphosphataemia (see section 4.8).

Cases of acute pancreatitis, which can be serious, have been reported (frequency: uncommon) under treatment with tigecycline (see section 4.8). The diagnosis of acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs or laboratory anomalies suggestive of acute pancreatitis. Most of the reported cases developed after at least one week of treatment. Cases have been reported in patients with known risk factors for pancreatitis. Patients usually improve after discontinuation of tigecycline. In cases where the development of pancreatitis is suspected, consideration should be given to the cessation of treatment with tigecycline.

Data on the use of tigecycline in the treatment of infections in patients with severe underlying diseases are limited.

In clinical studies in complicated skin and soft tissue infections, the most common type of infection in tigecycline-treated patients was cellulitis (59%), followed by major abscesses (27.5%). Patients with severe underlying disease, such as those that were immunocompromised, patients with decubitus ulcer infections, or patients that had infections requiring treatment for more than 14 days (for example, necrotising fasciitis), were not enrolled. A limited number of patients were enrolled with co-morbid factors such as diabetes (20%), peripheral vascular disease (7%), intravenous drug abuse (2%) and HIV-positive infection (1%). Limited experience is also available in treating patients with concurrent bacteraemia (3%). Therefore, caution is advised when treating such patients with tigecycline. The results of a large study in patients with diabetic foot infections showed that tigecycline was less effective than comparator, so tigecycline is not recommended for use in these patients (see section 4.1).

In clinical studies in complicated intra-abdominal infections, the most common type of infection in tigecycline-treated patients was complicated appendicitis (51%), followed by other infections less frequently reported such as complicated cholecystitis (14%), intra-abdominal abscess (10%), perforation of the intestine (10%) and gastric or duodenal ulcer perforation less than 24 hours after occurrence (5%). Among these patients, 76% has associated diffuse peritonitis (surgically apparent peritonitis). There was a limited number of patients with severe underlying disease such as immunocompromised patients, patients with and APACHE II score > 15 (4%), or with surgically apparent multiple intra-abdominal abscesses (10%).
Experience in patients with concurrent bacteraemia (6%) is also limited. Therefore, caution is advised when treating such patients with tigecycline.

Consideration should be given to the use of combination antibiotic therapy whenever tigecycline is to be administered to severely ill patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation or patients with incipient sepsis or septic shock (see section 4.8).
The effect of cholestasis on the pharmacokinetics of tigecycline has not been properly established.
Biliary excretion accounts for approximately 50% of total tigecycline excretion. Therefore, patients presenting with cholestasis should be closely monitored.
Prothrombin time or another suitable coagulation test should be used to monitor patients if tigecycline is administered to patients on anticoagulants (see section 4.5).

Cases of pseudomembranous colitis have been reported with nearly all antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to antibiotic treatment (see section 4.8).

The use of tigecycline may result in overgrowth of non-susceptible microorganisms, including fungi.

Patients should be carefully monitored during treatment, and appropriate measures should be taken in the event of super-infection (see section 4.8).

Results of studies in rats with tigecycline have shown bone discolouration. Tigecycline may be associated with permanent tooth discolouration in humans if used during tooth development (see section 4.8).

Paediatric population
TYGACIL should not be used in children under 8 years of age, because of the risk of tooth discolouration. The use of TYGACIL is not recommended in adolescents below 18 years due to the lack of data on safety and efficacy (see sections 4.2 and 4.8).”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J : Antiinfectives for systemic use
J01 : Antibacterials for systemic use
J01 A : Tetracyclines
J01 AA : Tetracyclines
J01 AA12 : Tigecycline

2.2. Medicines in the same therapeutic category

No antibiotic from the tetracycline group has the same indications as TYGACIL.

2.3. Medicines with a similar therapeutic aim

Medicines with a similar therapeutic aim are those that share the same indications, in particular: beta-lactams, quinolones, macrolides, glycopeptides, aminoglycosides, oxazolidinones and streptogramins.

3 REMINDER OF THE PREVIOUS OPINION

Opinion of the TC of 18 October 2006

Indications assessed:
"TYGACIL is indicated for the treatment of the following infections:

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

The official guidelines on the appropriate use of microbicides must be taken into consideration."

Actual benefit
"The conditions targeted by this medicinal product are immediately life-threatening or may cause fatal complications.

This proprietary medicinal product comes within the scope of curative treatment.

The efficacy/adverse effects ratio for this proprietary medicinal product is high in forms of low or moderate severity. In the case of severe forms, the efficacy/adverse effects ratio remains to be specified.

There are alternatives available for both indications, including for multi-resistant bacteria (MRSA, enterobacteria and, to a lesser degree, VRE).

Public health benefit
The public health burden imposed by complicated intra-abdominal infections resulting from treatment with TYGACIL is small, as is the burden imposed by complicated skin and skin structure infections, given the limited number of patients affected by these indications.
Providing new drugs to tackle the spread of pathogenic bacteria which have acquired antibiotic resistance mechanisms is a public health necessity.
In a patient population with a low or moderate level of severity, corresponding to the level in the studies, no additional impact is expected in terms of the reduction in the morbidity and mortality rates in relation to the treatments currently being used.
In the case of severe infections and/or infections caused by resistant bacteria, the data available are insufficient to be able to evaluate the impact TYGACIL is expected to have on morbidity and mortality rate reduction. A negative impact cannot be discounted where TYGACIL is used to treat the most severely affected patients.

The transposability of the experimental data is not guaranteed, given that the patients included in the trials were not representative of those likely to receive TYGACIL in practice. In the current state of knowledge, therefore, the response to this public health need has not been established.
Consequently, TYGACIL is not expected to have a public health benefit for these indications.

The actual benefit of this proprietary medicinal product is substantial."

Improvement in actual benefit (IAB):

"Based on the current data available, TYGACIL has not demonstrated that it can improve the actual benefit in relation to the treatments currently used for managing complicated skin and skin structure infections and complicated intra-abdominal infections (IAB V). However, it does provide an additional treatment resource for managing these infections."

Therapeutic use

"The standard treatment generally involves the use of antibiotics adapted to the bacteria actually identified or likely to be present. There are numerous possible options available, depending on the type of bacteria and their level of resistance. It is difficult at present to specify the role of TYGACIL due to insufficient documentation on its clinical efficacy in the case of severe infections and/or infections due to multi-resistant bacteria.

Based on the indications in the Marketing Authorisation, TYGACIL would be earmarked more specifically for patients requiring intravenous treatment in the case of multi-resistant bacterial infections sensitive to tigecycline and, particularly, when there is no alternative treatment available."

Target population

"The indications for TYGACIL are complicated intra-abdominal infections and complicated skin and soft tissue infections managed in the context of a hospitalized patient.

It is difficult at present to specify the target population for TYGACIL due to insufficient documentation regarding its clinical efficacy.

In practice, the number of patients likely to receive TYGACIL will probably be very limited as the percentage of patients eligible for this treatment is fairly low (complicated clinical forms of multiresistant bacteria infections sensitive to tigecycline and infections for which there is no alternative treatment available)."

4 ANALYSIS OF AVAILABLE DATA

The reassessment of the actual benefit of the propriety medicinal product TYGACIL was requested by the Transparency Committee in April 2011 because of concerns about this product from pharmacovigilance.

- A letter to healthcare professionals[1] dated 01/04/2011, relating to an observed increased mortality in the course of clinical studies carried out in indications both validated and not validated by the Marketing Authorisation (MA), specified that TYGACIL should only be used for the treatment of adults with cSSTI (excluding diabetic foot infections) and cIAI in the absence of an appropriate alternative.
- The first five-yearly renewal of the Marketing Authorisation by the European Commission for the propriety medicinal product TYGACIL (tigecycline) 50 mg was granted on 6 May 2011. The main changes to the Summary of Product Characteristics are as follows:

Change to section 4.1: Therapeutic indications (the changes introduced are shown below in bold):

"TYGACIL is indicated in adults for the treatment of the following infections:
- Complicated skin and soft tissue infections, excluding diabetic foot infections;
- Complicated intra-abdominal infections.

TYGACIL must not be used except in the absence of an appropriate alternative treatment.

Change to section 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 higher mortality rate among TYGACIL-treated patients has been observed compared with those on the comparator treatment. The causes of these findings remain unknown, but poorer efficacy than the 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 a complicated skin and soft tissue infection or a complicated intra-abdominal infection is identified after initiation of TYGACIL therapy, consideration should be given the use of an alternative antibiotic therapy that has been demonstrated to be efficacious in the treatment of this new infection.

TYGACIL is only indicated for the treatment of cSSTI and cIAI in adults. The use of TYGACIL in non-approved indications is not recommended."

[1] IMPORTANT PHARMACOVIGILANCE INFORMATION – TYGACIL- AFSSAPS. Letter to healthcare professionals concerning the increased mortality observed in the course of clinical studies with Tygacil® (*tigecycline*). www.afssaps.fr/content/download/32910/432314/.../lp-110401-Tygacil.pdf

4.1. Clinical data

4.1.1. Reminder of the conclusions of the previous opinion (Opinion of the TC of 18 October 2006)

"The non-inferiority clinical trials (delta threshold = 15%), carried out for complicated skin and skin structure infections *versus* the vancomycin/aztreonam combination (studies 300-WW and 305-WW) and for complicated intra-abdominal infections *versus* imipenem/cilastatin (studies 301-WW and 306-WW), with a potential treatment duration of up to 14 days, highlighted that TYGACIL's clinical efficacy was not inferior to that of the comparators used. However, the findings of these studies are debatable in terms of clinical relevance.

- **In complicated skin and soft tissue infections**

The clinical success rates (cure and clinical improvement) in the clinically-modified intention-to-treat (c-mITT) population were around 76% (95% CI[2]: -9.0 ; 6.1) in study 300 and around 85% (95% CI: -9 ; 3.8) in study 305. However, the comparators used (vancomycin plus aztreonam) are not the reference comparators. The most common infection in the patients treated with TYGACIL was cellulitis (59%), followed by major abscesses (27.5%). The number of diabetic patients with a foot infection (5%), patients with concomitant bacteraemia (3%) and those with comorbidity factors such as diabetes (20%), peripheral vascular disease (7%), intravenous drug use (2%) and HIV infection (1%) was limited. The following were not included: patients with an underlying pathology, such as immunodepressed patients, patients with infected bedsores or patients with an infection requiring treatment for more than 14 days (*e.g*. necrotising fasciitis), especially when suspected of being due to methicillin-resistant *Staphylococcus aureus* (MRSA).

Consequently, the data available do not make it possible to position this proprietary medicinal product adequately in the therapeutic management of severe infections and/or infections caused by resistant bacteria, compared with regularly effective drugs, such as penicillinase-resistant beta lactam antibiotics.

- **In complicated intra-abdominal infections:**

The clinical success rates (cure and clinical improvement) in the m-mITT population were 73.5% in the TYGACIL group *versus* 78.2% in the comparator group (95% CI9: -11.8 ; 2.3) in study 301 and 86.6% *versus* 84.6% (95% CI: -3.7 ; 7.7) in study 306. The most common infection in the patients treated with TYGACIL was complicated appendicitis (51%), followed by complicated cholecystitis (14%), intra-abdominal abscesses (10%), intestinal perforations (10%) and perforations of gastric or duodenal ulcers of less than 24 hours (5%). 76% of these patients had associated diffuse peritonitis (identified during surgery). The mean APACHE II score was 6 and only 4% of patients had an APACHE II score > 15, which represents a low level of severity. The number of patients with a severe underlying pathology, such as immunodepressed patients, patients with multiple intra-abdominal abscesses identified surgically (10%) or with concomitant bacteraemia (6%) was limited.

Consequently, the data available does not make it possible to position this proprietary medicinal product adequately in the therapeutic management of severe infections and/or infections caused by resistant bacteria, compared with regularly effective drugs, such as the combination of amoxicillin with a regularly effective beta-lactamase inhibitor for relatively mild secondary forms of peritonitis (acute appendicitis, perforated ulcer) or the combination of active antibiotics in the case of enterobacteria (aminoglycosides, cephalosporins, ureidopenicillin) and a nitroimidazole in the case of larger lesions (submesocolic peritonitis) to guarantee efficacy in relation to Gram-negative anaerobic bacteria from the *Bacteroides fragilis* group, which are often resistant to penicillins and cephalosporins.

The most common adverse effects reported with tigecycline were nausea (20%) and vomiting (14%), which were the most common reason for discontinuing treatment. They were reversible, of mild to moderate severity, and appeared after one to two days of treatment. They were reversible, of slight to moderate intensity and occurred after 1 to 2 days of treatment. A few (3) cases of pancreatitis were reported during the trials. It should be noted that these cases will be particularly well-monitored as part of the risk management plan, given the known association

[2] Confidence interval of the TYGACIL – comparator difference

between pancreatitis and tetracyclines, which have a similar structure to that of the glycylcyclines."

4.1.2. Update of the efficacy data

The company submitted the results of four new clinical studies (Table 1).

Table 1: Methodology of the newly presented studies

Study No.	Type of study	Treatments	Dose / frequency	N
Complicated intra-abdominal infections (cIAI)				
316-CN Nov 2005 / Dec 2006	Controlled, randomised, open phase III study comparing the safety and efficacy of tigecycline versus imipenem-cilastatin in the treatment of hospitalised (Chinese) patients with cIAI.	Tigecycline	Tigecycline (IV): initial loading dose of 100 mg followed by doses of 50 mg every 12 h	97
		Imipenem	Imipenem (IV): maximum of 500 mg every 6 h, depending on the weight and creatinine clearance	102
315-WW Nov 2005 / Sep 2008	Controlled, randomised, open phase IV study comparing the tolerance and efficacy of tigecycline versus ceftriaxone sodium plus metronidazole in the treatment of hospitalised patients with cIAI.	Tigecycline	Tigecycline (IV): initial loading dose of 100 mg followed by doses of 50 mg every 12 h	232
		Ceftriaxone + metronidazole	Ceftriaxone IV: 2 g Metronidazole IV: 1 to 2 g daily, divided into several doses	235
400-WW Sep 2005 / Feb 2008	Controlled, randomised, open phase IV study comparing the tolerance and efficacy of tigecycline versus ceftriaxone sodium plus metronidazole in the treatment of hospitalised patients with cIAI.	Tigecycline	Tigecycline (IV): initial loading dose of 100 mg followed by doses of 50 mg every 12 h	236
		Ceftriaxone + metronidazole	Ceftriaxone IV: 2 g Metronidazole IV: 1 to 2 g daily, divided into several doses	231
Complicated skin and soft tissue infections (cSSTI)				
900-WW Sep 2006 / Sep 2008	Controlled, randomised, open phase IV study comparing the tolerance and efficacy of tigecycline and ampicillin-sulbactam or amoxicillin-clavulanic acid in the treatment of cSSTI.	Tigecycline	Tigecycline (IV): initial loading dose of 100 mg followed by doses of 50 mg every 12 h	268
		Ampicillin-sulbactam **or** Amoxicillin-clavulanic acid **±** Vancomycin or teichoplanin if infection with methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected or confirmed during the 72 h after inclusion	Ampicillin-sulbactam: 1.5 to 3.0 g every 6 h. Amoxicillin-clavulanic acid: 1.2 g IV every 9-8 h	263
			Vancomycin IV: 1 g every 12 hours Teicoplanin IV: loading dose of 400 mg then 200 mg daily	

- Results of study 316-CN[3]

The principal objective of this study was to evaluate the tolerance and clinical efficacy of tigecycline versus imipenem in the treatment of hospitalised patients with complicated intra-abdominal infections.

[3] Chen, Z. et al. Efficacy and safety of tigecycline monotherapy vs. imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. BMC Infect Dis 2010; 10: 217.

The patients included had an APACHE score ≤ 15 (mean score 4.25 in the tigecycline group and 3.79 in the imipenem group). Complicated appendicitis was the most frequent clinical diagnosis (76% of cases).

The primary efficacy endpoint was the clinical cure rate at the assessment visit (12 to 37 days after treatment) in the microbiologically evaluable populations (ME) and in the microbiological modified intention to treat population (m-mITT).

The clinical cure rates were:

- in the ME population: 86.5% (45/52) for tigecycline versus 97.9% (47/48) for imipenem (difference: -11.4%; 95% CI [-23,5; 0,7]),
- in the m-mITT population: 81.7% (49/60) for tigecycline versus 90.9% (50/55) for imipenem (difference: -9.2%; 95% CI [-23.4; 4.9]).

For complicated appendicitis, the most frequent clinical diagnosis, the clinical cure rate in the ME population was 87.0% (40/46) for tigecycline versus 100% (45/45) for imipenem (difference: - 13%; 95% CI [-27.0; -0.6]).

The microbiological eradication rates were similar to the clinical cure rates observed in the two treatment groups: 86.5% (45/52) for tigecycline versus 97.9% (47/48) for imipenem. For *Escherichia coli*, the bacterium most frequently isolated, the eradication rate was 88.1% (37/42) for tigecycline versus 97.7% (43/44) for imipenem.

Even though the study was not designed with the statistical power required to test the non-inferiority of tigecycline versus imipenem, it should be noted that the cure rates were lower in the tigecycline group than in the imipenem group. The response rates observed in the tigecycline group are of the same order as those observed in the phase III pivotal studies.

- Results of studies 315-WW and 400-WW. The results of study 400-WW have been the subject of a publication.[4]

The principal objective of these studies was to evaluate the tolerance and non-inferiority (delta threshold = 15%) of the clinical efficacy of tigecycline versus the ceftriaxone plus metronidazole combination in the treatment of hospitalised patients with complicated intra-abdominal infections.
The most frequent clinical diagnosis in the two studies was complicated appendicitis (48% in study 315 and 52% in study 400). The mean APACHE II score was 6, and the majority of patients (about 80%) has a score of less than 10.
The mean duration of treatment was 7 days (2 to 15 days).

The primary efficacy endpoint was the clinical cure rate in the clinically evaluable population (CE) at the assessment visit (8 to 44 days after the last administration of the treatment).

[4] Towfigh, S. et al. A multicentre, open-label, randomised comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalised subjects with complicated intra-abdominal infections. Clin Microbiol Infect. 2010; 16 (8): 1274-81.

In these studies, tigecycline was non-inferior to the ceftriaxone/metronidazole combination at the pre-established threshold of non-inferiority (-15%). In the CE population, the cure rates were:

- in study 315-ww: 81.8% (162/198) for tigecycline versus 79.4% (150/189) for the ceftriaxone/metronidazole combination.
- in study 400-ww: 70.4% (133/189) for tigecycline versus 74.3% (139/187) for the ceftriaxone/metronidazole combination.

The difference in the clinical response between the two treatments in each study is summarised in Table 2.

Table 2: Difference in clinical response between tigecycline and ceftriaxone/metronidazole (studies 315 and 400)

	Difference (tigecycline – ceftriaxone/metronidazole) Clinical response (success rate) p % (95% CI)	
	Study 315	**Study 400**
Clinically evaluable population	2.4 (-5.6; 10.5)	-4.0 (-13.1; 5.1)
Microbiologically evaluable population (ME)	1.8 (-8.8; 12.5)	-3.4 (-14.5; 7.8)

As the two studies were methodologically similar, a pooled analysis was carried out. In the CE population, the cure rate was 76.2% (295/387) for tigecycline versus 76.9% (289/376) for the ceftriaxone/metronidazole combination.

The clinical responses observed in study 400 were all lower than those observed in study 315. Only study 315 reached the threshold of non-inferiority of -10% proposed in the recommendations on the assessment of antibacterials.[5]

The two studies differed markedly in the proportion of patients with a polymicrobial infection (54% in study 315 and 80% in study 400). In the tigecycline group, the response was different in the two studies, with a higher percentage microbiological eradication in study 315 than in study 400. This difference was more pronounced for monomicrobial infections (84.1% clinical success in study 315 and 56.3% in study 400). In polymicrobial infections, the response rate for tigecycline was 72.3% in study 315 and 63.4% in study 400. The response rates for ceftriaxone/metronidazole were similar in the two studies in both monomicrobial infections (study 315: 76.6%; study 400: 72.2%) and polymicrobial infections (study 315: 68.2%; study 400: 65.6%). It should be noted that the percentage super-infection was higher in the tigecycline group than in the comparator group (study 315: 2% versus 0%; study 400: 3.7% versus 1.3%).

[5] The European Agency for the Evaluation of Medicinal Products (EMEA): Note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections. London, 22 April 2004 CPMP/EWP/558/95 version 1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003417.pdf

- Results of study 900-WW

The principle objective of this study was to evaluate the tolerance and non-inferiority (delta threshold = 15%) of the clinical efficacy of tigecycline versus ampicillin-sulbactam or amoxicillin-clavulanic acid in the treatment of patients with complicated skin and soft tissue infections (cSSTI).

The primary efficacy endpoint was the clinical cure rate in the clinically evaluable population at the assessment visit (10 to 28 days after the last administration of the treatment).

The mean duration of treatment was 8 days (1 to 18 days).

The most frequent clinical diagnoses were “cellulitis” (64.4%), “major abscess” (19.5%) and “infected ulcer” (10.4%)

In this study, tigecycline was non-inferior to the comparator treatments in the population studied, with a clinical cure rate of 77.5% (162/209) in the tigecycline group versus 77.6% (152/196) in the comparator group (difference 0.0; 95% CI [-8.7; 8.6]).

4.1.3. Update of the tolerance data

4.1.3.1. Tolerance data from the new clinical studies

Study 316-CN

The tolerance data were evaluated for 97 patients who were given at least one dose of tigecycline and 102 patients who were given at least one dose of imipenem.
The incidence of adverse events was 80.4% in the tigecycline group versus 53.9% in the imipenem group; this difference was mainly due to gastrointestinal adverse events (nausea and vomiting). These adverse effects were considered to be of moderate to low severity in the majority of cases and rarely resulted in the interruption of treatment (two patients in each group). Nine cases of serious adverse events were reported (tigecycline 8.2% [eight cases], imipenem 1% [one case]); most often abnormal healing (tigecycline 3.1% [three cases], imipenem 0%). These adverse events were not thought to be due to the study treatments.
Adverse events thought to be due to the treatment were more frequent in the tigecycline group than in the imipenem group (55.7% versus 41.2%), and were mainly nausea (20.6% versus 2%) and vomiting (10.3% versus 1%).
One patient treated with tigecycline died one day after the start of treatment; this death was not thought to be due to the treatment.
Abnormal laboratory results: There were more cases of bilirubinaemia in patients treated with tigecycline than in those treated with imipenem (21.6% versus 11.8%).

Study 315-WW

The tolerance data were evaluated for 232 patients treated with tigecycline and 235 patients treated with the combination of ceftriaxone and metronidazole.
The incidence of adverse events was 63.4% in the tigecycline group versus 61.7% in the ceftriaxone/metronidazole group. The incidence of adverse events thought to be due to the treatment was higher in the TYGACIL group (21.6% versus 12.8%); the most frequent were gastrointestinal adverse events (15.5% versus 8.9%), predominantly “nausea and vomiting” (10.8% versus 4.7%). These events were considered to be of mild to moderate in intensity in the majority of cases.
The incidence of serious adverse events was similar in the two treatment groups (tigecycline 15.9%; ceftriaxone/metronidazole 16.2%); the most frequent were: infection (2.4%), abnormal healing (2.4%), sepsis (1.9%), pneumonia (1.9%) and abscess (1.3%). Discontinuations of treatment due to the occurrence of adverse events were 7.8% in the tigecycline group versus 6.4% in the ceftriaxone plus metronidazole group.
Eighteen patients died during the study (tigecycline 11; ceftriaxone/metronidazole 7). These deaths were considered to be “probably not due” or “definitely not due” to the treatment.

Study 400-WW

The tolerance data were evaluated for 236 patients treated with tigecycline and 231 patients treated with the combination of ceftriaxone and metronidazole.
The incidence of adverse events was similar in the two treatment groups (83.5% versus 82.3%). The most frequent adverse events were “nausea” and “vomiting”, and were mild to moderate in intensity in the majority of cases; treatment was stopped because of nausea in six (2.5%) patients treated with tigecycline and one (0.4%) treated with ceftriaxone/metronidazole and in two patients (one patient in each group) because of vomiting.
The global incidence of serious adverse events was similar in the two treatment groups (tigecycline 21.6%; ceftriaxone plus metronidazole 21.2%); the most frequent were abscess (6.6%), infection (1.5%), breathing difficulty (1.5%), abdominal pain (1.3%) and intestinal obstruction (1.3%).
Seven patients died during the study (tigecycline four; ceftriaxone/metronidazole three). None of the deaths was attributed to the treatment.

Study 900-WW

The tolerance data were evaluated for 268 patients treated with tigecycline and 263 patients treated with the comparator (ampicillin-sulbactam or amoxicillin-clavulanic acid ± vancomycin or teicoplanin).
The incidence of adverse events was higher in the tigecycline group than in the comparator group (75.7% versus 66.2%). Gastrointestinal adverse events (nausea, diarrhoea and vomiting) were the most frequent (59% versus 31.6%). These events were considered to be mild to moderate in intensity in the majority of cases. The incidence of serious adverse events was 14.2% in the tigecycline group versus 11% in the comparator group and discontinuations of treatment due to the occurrence of an adverse event were 6% versus 3%.
Eleven patients died during the study (6 patients in the tigecycline group and 5 patients in the comparator group). These deaths were considered to be “probably not due” or “definitely not due” to the treatment.

4.1.3.2. Global analysis of the mortality data

A pooled analysis of the morality data was carried out on the basis of 13 phase III or IV clinical studies carried out since August 2001 both in indications validated and not validated by the marketing authorisation (Table 3). This analysis showed a higher mortality rate among the patients treated with Tygacil than among those treated with the comparators: 3.9% (147/3788) versus 2.9% (105/3646), with an overall absolute difference in the risk of mortality of 1% (95% CI: [0.2-1.8]).
The difference in risk varies between the different types of infection. The indications nosocomial pneumonia (NP) and resistant pathogens (RP) presented the highest risk of mortality. A greater risk was observed in patients with ventilator-associated pneumonia, a subgroup of patients with nosocomial pneumonia.

Table 3**:** Mortality rates in the phase III and IV clinical studies carried out since August 2001 in validated and non-validated indications

Mortality rate classified according to type of infection			
Type of infection	**TYGACIL, n/N (%)**	**Comparators, n/N (%)**	**Difference (95% CI)**
cSSTI*	12/834 (1.4)	6/813 (0.7)	0.7 (-0.3; 1.7)
cIAI*	42/1382 (3.0)	31/1393 (2.2)	0.8 (-0.4; 2.0)
CAP	12/424 (2.8)	11/422 (2.6)	0.2 (-2.0; 2.4)
NP	66/467 (14.1)	57/467 (12.2)	1.9 (-2.4; 6.3)
Non-VA[a]	41/336 (12.2)	42/345 (12.2)	0.0 (-4.9; 4.9)
VA[a]	25/131 (19.1)	15/122 (12.3)	6.8 (-2.1; 15.7)
RP	11/128 (8.6)	2/43 (4.7)	3.9 (-4.0; 11.9)
DFI	7/553 (1.3)	3/508 (0.6)	0.7 (-0.5; 1.8)
Total	**150/3788 (3.9)**	**110/3646 (2.9)**	**1 (0.2; 1.8) ****

cSSTI: Complicated skin and soft tissue infections; cIAI: Complicated intra-abdominal infections; CAP: Acute community-acquired pneumonia; NP: Nosocomial pneumonia; DFI: Diabetic foot infection; RP: Resistant pathogen
* Approved indications
** Difference between the percentage mortality among patients in the tigecycline group and those in the comparator group
[a]: Subgroup of the NP population (VA = ventilator-associated pneumonia)

4.1.3.3. Clinical experience according to the SPC (correction of the MA of 24 August 2011)

a. Summary of the tolerance profile

The total number of patients treated with tigecycline in phase III clinical studies was 1415. Adverse reactions were reported in approximately 41% of patients treated with tigecycline. Treatment was discontinued due to adverse events in 5% of patients.

In clinical studies, the most common treatment-related adverse events were nausea (20%) and vomiting (14%). They were reversible, of mild to moderate severity, and usually occurred early (after one to two days of treatment).
In phase III clinical studies, serious adverse events due to infections were more frequent in patients treated with tigecycline (6.7%) than in patients who received the comparator treatment (4.6%). In relation to sepsis/septic shock, significant differences were observed between tigecycline (1.5%) and the comparators (0.5%).

Abnormal ASAT and ALAT levels after treatment were reported more frequently among patients treated with TYGACIL than among patients who were given the comparator treatment, and they were also reported more frequently during treatment.

In all the phase III and IV studies carried out in complicated skin and soft tissue infections and complicated intra-abdominal infections taken together, the mortality rate was 2.3% (52/2216) in patients treated with tigecycline and 1.5% (33/2206) in patients treated with the comparators.

Adverse events reported with TYGACIL, including clinical studies and post-marketing experience, are listed below.
Frequency categories are expressed as follows: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1000, < 1/100); Rare (≥ 1/10,000, < 1/1000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data). For adverse effects identified from post-marketing experience with TYGACIL derived from spontaneous reports for which the frequency cannot be estimated, the frequency is classified as “not known”.

b. Tabulated summary of adverse effects

Infections and infestations:

Common: Pneumonia, abscess, infections

Uncommon: Sepsis/septic shock

Blood and lymphatic system disorders:

Common: Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)

Uncommon: Increased INR

Not known: Thrombocytopenia

Immune system disorders:

Not known: Anaphylaxis/anaphylactoid reactions (see sections 4.3 and 4.4)

Metabolic and nutritional disorders:

Common: Hypoglycaemia

Uncommon: Hypoproteinaemia

Nervous system disorders:

Common: Dizziness

Vascular disorders:

Common: Phlebitis

Uncommon: Thrombophlebitis

Gastrointestinal disorders:

Very common: Nausea, vomiting, diarrhoea

Common: Abdominal pain, dyspepsia, anorexia

Uncommon: Acute pancreatitis (see section 4.4)

Hepatobiliary disorders:

Common: Elevated serum levels of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT), hyperbilirubinaemia

Uncommon: Jaundice, liver injury, mostly cholestatic

Not known: Hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders:

Common: Pruritus, rash

Not known: Severe skin reactions, including Stevens-Johnson syndrome

General disorders and administration site conditions:

Common: Headache

Uncommon: Injection site reaction, inflammation, pain, oedema or phlebitis

Investigations:

Common: Elevated serum amylase, elevated blood urea nitrogen

See the SPC for the description of certain adverse effects (antibiotic class effects, tetracycline class effects).

4.2. Data from use in clinical practice (protocol 3074A1-4448). Unpublished study

The company submitted a prospective observational study describing the efficacy, tolerance and methods of use of tigecycline in 26 French intensive care units. One hundred and fifty six adult patients (64.1% men, mean age = 60 years) were included in the study and were given tigecycline, mostly for intra-abdominal infection (56.4%; of whom 69.3% had generalised peritonitis, 17.7% localised peritonitis and 22.1% abscesses), followed by another infection (35.9%; located in the lungs in 67.9% of cases) and skin and soft tissue infection (18.6%). The most frequent underlying diseases were immunosuppression (33.3%), diabetes (19%) and chronic renal failure (10%). Tigecycline was prescribed as first-line therapy in 73 patients (46.8%), as second-line therapy in 72 patients (46.2%) and as third-line therapy in 11 patients (7.1%). In the majority of cases (67.3%), tigecycline was prescribed as part of a combination, mostly with an aminoglycoside (26%), a penicillin (16%) and a fluoroquinolone (10%). The principal reasons for prescription were polymicrobial infection (55.1%) or a suspected or identified multiresistant organism (40.4%), renal insufficiency (17.9%), multiple infected sites (15.4%) or preceding therapeutic failure (12%). The bacteria most frequently isolated at the start of treatment were gram-positive cocci (50%, 78/127) and enterobacteria (50%, 78/127; mainly *E. coli* 28.2%), followed by other pathogens (20.5%; of which *S. maltophilia* 5.1% and *P. aeruginosa* 3.8%) and anaerobes (9%, 14/127).
In terms of severity, the MacCabe score[6] showed that the majority of patients (65.8%) did not have a fatal disease; 8.4% had a disease expected to be fatal in less than one year, and 25.8% a disease expected to be fatal in between one and five years.
The mean duration of treatment with tigecycline was 10.2 ± 8.8 days (range: 1.0-78.0 days). The tigecycline treatment was discontinued prematurely in 66 (42%) patients, mainly because of a resistant strain (8.3%), clinical failure (9.0%), de-escalation (12.8%), death (9.0%) or a new infection (2.6%).

Efficacy

At the end of treatment, the clinical success rate (cure) was 59.6% (93/156), 95% CI [51.5; 67.4]. Failure was reported in 18% (28/156), comprising 4 fatalities and 12 cases of persistence of the initial clinical signs requiring a change of antibiotic treatment. The global success rate (seven days after the end of the treatment or at the end of hospitalisation) was 53% (77/145), 95% CI [44.6; 61.4].

Adverse effects

Of the 156 patients given tigecycline, 36 (23.1%) had at least one adverse event (AE), and, of these, 26 patients (16.7%) had at least one serious AE. The most frequent AEs were: multisystem organ failure (5.8%), septic shock (3.8%), vomiting/nausea and cholestasis (1.9%); other AEs were reported with a global incidence ≤ 1.3%.
There were 18 fatalities during the study (11.5%): 16 patients (10.3%) died because of an AE at the end of treatment; there were 2 additional deaths classified as possibly due to the treatment.

Authors' conclusion

This observational study describes the use of tigecycline in intensive care units and confirms that this antibiotic could be an interesting option for the treatment of complicated intra-abdominal infections (and, to a lesser degree, complicated skin and soft tissue infections) specifically caused by enterobacteria (E. coli) and gram-positive cocci. No major new tolerance concerns were identified.

4.3. Conclusion

The new phase III and IV studies (studies 316, 315, 400 and 900) carried out in complicated intra-abdominal infections (cIAI) and complicated skin and soft tissue infections (cSSTI) were essentially carried out, like the earlier studies, in populations with infections of mild to moderate severity.

[6] Predictive mortality score used particularly in intensive case: the patient's survival time in the presence of the underlying disease is evaluated: at less than one year (MacCabe 3), between one and five years (MacCabe 2), non-fatal disease or more than five years (MacCabe 1) or no disease (MacCabe 0).

In study 316, carried out in Asian patients with cIAI, the clinical cure rate was 81.7% (49/60) for tigecycline versus 90.9% (50/55) for imipenem (difference: -9.2; 95% CI [-23.4; 4,9]). Even though the study was not designed with the statistical power required to test the non-inferiority of tigecycline versus imipenem, this result suggests that tigecycline has lower efficacy in the population studied.

In two other studies with similar methodologies (studies 315 and 400), carried out in patients with cIAI, tigecycline was non-inferior (threshold of non-inferiority = -15%) to the combination of ceftriaxone and metronidazole. The clinical cure rates were:

- study 315: 81.8% (162/198) for tigecycline versus 79.4% (150/189) for the combination of ceftriaxone and metronidazole (difference: 2.4; 95% CI [-5.6; 10.5]),
- study 400: 70.4% (133/189) for tigecycline versus 74.3% (139/187) for the combination of ceftriaxone and metronidazole (difference: -4.0; 95% CI [-13.1; 5.1])

The observed clinical responses in study 400 were nevertheless lower than those observed in study 315. Only study 315 reached the threshold of non-inferiority of -10% proposed in the CHMP recommendations on the assessment of antibacterials.[5]

In study 900, carried out in patients with cSSTI, tigecycline was non-inferior (threshold of non-inferiority = -15%) to the ampicillin-sulbactam or amoxicillin-clavulanic acid combinations, with a cure rate of 77.5% (162/209) in the tigecycline group versus 77.6% (152/196) in the comparator group (95% IC of the difference [-8.7; 8.6]).

Overall, the efficacy and tolerance profile observed in the new studies with tigecycline is similar to that observed in the earlier studies.
In all the phase III and IV studies carried out in the indications of the Marketing Authorisation taken together, tigecycline is not more effective than the comparators studied, with notably more frequent gastrointestinal disorders (nausea, vomiting, diarrhoea). The mortality rate was 2.3% (52/2216) in patients treated with tigecycline and 1.5% (33/2206) in patients treated with the comparators. The efficacy and tolerance data in patients with severe infections or infections due to multiresistant bacteria and in patients with severe underlying diseases are still limited.

An analysis of the mortality on the basis of 13 phase III and IV clinical studies carried out since August 2001 in indications both validated and not validated by the Marketing Authorisation, has demonstrated a higher mortality rate among the patients treated with tigecycline than among the patients treated with the comparators **(**3.9% versus 2.9%; overall absolute difference in the risk of mortality of 1% (95% CI: [0.2; 1.8]). The causes of this higher mortality rate remain unknown, but the possibility that tigecycline is less effective cannot be ruled out.
As a consequence, the CHMP has recommended measures aimed at minimising the risk of fatal outcomes in sensitive or gravely ill patients. These measures are:

- changes to the SPC:
  - to indicate that Tygacil may only be used in adults, in the approved indications, and in the absence of appropriate alternative treatments,
  - to warn of the possible higher mortality rate and the need to monitor patients closely and institute an alternative treatment in the event of super-infection.
- implementation of a risk minimisation plan, in particular for superinfections, for treatment failure and for off-label use,
- institution of a tolerance study.

The restriction of the indication is consistent with the previous opinion of the Transparency Committee (opinion of 18 October 2006).
The Transparency Committee takes note of the new data within the framework of the re-assessment of the actual benefit.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

The nature of new data presented is not such as to change the conclusions of the previous opinion of the Transparency Committee (opinion of 18 October 2006):

The disorders addressed by this proprietary medicinal product are either immediately life-threatening to the patient or life-threatening after complications.

This proprietary medicinal product is intended for curative treatment.

In the two indications, the efficacy/adverse effects ratio of this medicinal product is substantial for forms of mild or moderate severity. For severe forms, the efficacy/adverse effects ratio remains to be determined.

Alternatives exist, including for multiresistant bacteria (MRSA – and, to a lesser degree, VRE and certain enterobacteria).

Public health benefit

The public health burden of complicated intra-abdominal infections requiring treatment with TYGACIL is low, as is that of complicated skin and soft tissue infections, bearing in mind the probably limited number of patients affected by these indications.

The availability of new compounds to address the spread of pathogenic bacteria that have acquired resistance mechanisms to antibiotics is a public health need.

Among the population of patients with a low to moderate level of severity corresponding to that in the studies, there would not be expected to be any supplementary impact on the reduction in morbidity/mortality compared with treatments in current use.

In severe infections and/or infections due to resistant bacteria, the available data are insufficient to evaluate the expected impact of TYGACIL on the reduction in morbidity/mortality. In the most seriously affected patients, who have not been studied with TYGACIL, it is not possible to rule out a negative impact.

It is not certain that the experimental data are transposable, as the patients included in the studies were not representative of those likely to receive TYGACIL in practice. Thus, a response to the public health need has not been established in the current state of knowledge.

Consequently, it is not expected that TYGACIL would benefit public health in these indications.

The actual benefit of the propriety medicinal product **remains substantial** only in restricted clinical situations, complicated clinical forms of skin and soft tissue infections and intra-abdominal infections involving bacteria sensitive to tigecycline and when alternative treatments are considered inappropriate.

5.2. Improvement in actual benefit (IAB)

Not applicable

5.3. Therapeutic use

The normal treatment generally comprises antibiotics suitable for use against identified or probable bacteria. There are numerous possible choices, depending on the bacteria and their level of resistance.

Among the indications in the Marketing Authorisation, TYGACIL should be reserved specifically for patients requiring treatment by the intravenous route, in cases of infection with bacteria sensitive to tigecycline and when alternative treatments are considered inappropriate.

5.4. Target population

The number of patients who might receive TYGACIL would be limited, in view of the fairly low percentage of patients who would be eligible for this treatment (complicated clinical conditions involving bacteria sensitive to tigecycline and when no alternative treatment exists).

In the antibiotic market, TYGACIL sales represent 14,365 days of treatment as a moving annual total (source: Gers Hop April 2011). As the mean duration of treatment with TYGACIL is about 10 days, and the number of patients currently being treated with TYGACIL is estimated at about 1400 per year.[7] This estimate does not permit a distinction to be drawn between prescriptions covered by the validated indications and off-label prescriptions. As a guide, according to the results of a study into the use of TYGACIL in Europe carried out on the basis of 23,714 hospitalised patients in 2008, 38.7% of the patients were treated for indications in the Marketing Authorisation and 61.4% off-label.[8]

By extrapolation, the number of patients treated with Tygacil for indications covered by the Marketing Authorisation is estimated at about 500.

5.5. Transparency Committee recommendations

The transparency Committee recommends continuing inclusion on the list of medicines approved for hospital use and various public services in the indications and at the dosages specified in the Marketing Authorisation.

7 Estimate carried out by the company

8 Source: Transparency dossier. Frequency of off-label use reported by the company. The data are from the database of Arlington Medical Resources (AMR) set up to monitor the consumption of antibiotics in hospitals in five European countries (France, Germany, Italy, Spain and the United Kingdom).