HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 October 2006

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

Applicant: WYETH PHARMACEUTICALS FRANCE

tigecycline

List I
Medicinal product requiring hospital prescription.

Date of Marketing Authorisation: 24 April 2006
European Marketing Authorisation based on the centralised procedure

Reason for request: Inclusion on the list for hospital use

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

tigecycline

1.2. Background

TYGACIL is a new broad-spectrum antibiotic belonging to a tetracycline subgroup: the glycylcyclines.

1.3. Indication

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.

1.4. Posology and method of administration

Posology

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 the 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 must be reduced to 25 mg every 12 hours after an initial dose of 100 mg. Patients with severe hepatic impairment (Child Pugh C) must be treated with caution and monitored for treatment response.

Renal insufficiency

No dosage adjustment is necessary in patients with renal impairment or receiving haemodialysis treatment.

Elderly patients

No dosage adjustment is necessary in elderly patients.

Children

TYGACIL is not recommended for use in children and adolescents below 18 due to the lack of on safety and efficacy.

Method of administration

TYGACIL is administered only by intravenous infusion over 30 to 60 minutes.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J : Anti-infectives 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 in the tetracycline group has the same indications as TYGACIL.

2.3. Medicines with a similar therapeutic aim

Medicinal products with the same therapeutic objective are those which share the same indications, in particular: beta-lactam antibiotics, quinolones, macrolides, glycopeptides, aminoglycosides, oxazolidinones, synergistins.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. Complicated skin and skin structure infections (cSSSI)

The TYGACIL clinical development program has included 2 pivotal non-inferiority studies (studies 300-US/CA and 305-WW), whose principal objective was to compare the efficacy and safety of tigecycline with those of the vancomycin/aztreonam combination for the treatment of complicated[1] skin infections, with a potential treatment duration of up to 14 days. TYGACIL would be considered non-inferior to the comparator treatment if the lower limit of the 95% confidence interval of the difference between the clinical success rates of TYGACIL and the comparator treatment was greater than -15%.

- Inclusion and exclusion criteria

To be included in the study, patients had to be hospitalised, be aged at least 18 years and require treatment with IV antibiotics for at least 5 days.

They had to have:

- a deep soft tissue infection;
- or an infection requiring surgery;
- or an infection associated with an underlying illness such as:
    - diabetes
    - peripheral vascular disease
    - peripheral neuropathy
    - venous insufficiency of the lower limbs.

In addition to having an infection, subjects also had to present with at least two of the following signs or symptoms: drainage or discharge, fever, rash, oedema, localised flushes, pain and/or leucocytosis (> 10 000/mm^3).

Patients with necrotising fasciitis, gangrene, infected bedsores or neutropenia could not be included in these studies.

[1] Complication criteria (according to the FDA): a deep soft tissue infection or infection requiring surgery, pre-existing skin lesions, any underlying condition whose effects could have an impact on the release of the drug at lesion level or induce an immunological response or prevent scarring.

➢ Treatments :

The eligible patients were randomised to receive:

- either TYGACIL, administered via intravenous infusion (for 30 minutes) at the initial dose of 100 mg, followed by a dose of 50 mg every 12 hours;
- or a combination of vancomycin/aztreonam administered via intravenous infusion (for 30 minutes) : 1g of vancomycin followed by an intravenous infusion of 2g of aztreonam every 12h.

➢ Primary endpoint:

The primary endpoint was the clinical response (cure or failure), assessed after the end of treatment (for a minimum period of 12 days and a maximum period of 92 days) in the clinically evaluable (CE)[2] population or in the clinically modified intention-to-treat (c-mITT)[3] population. A cure was defined as the complete resolution or improvement of the clinical signs and symptoms caused by the infection, such that no further antibiotic treatment was necessary.

➢ Results

- Study population and treatment procedures

	Study 300		**Study 305**	
	TYGACIL	**Vancomycin + aztreonam**	**TYGACIL**	**Vancomycin + aztreonam**
Randomised (ITT population)	295	288	275	271
Randomised not treated	3	7	1	2
Modified intention-to-treat (mITT)[4] population n (%)[a]	292 (99)	281 (97.6)	274 (99.6)	269 (99.3)
Clinically modified intention-to-treat (c-mITT) population n (%)[a]	277 (93.9)	260 (90.3)	261 (94.9)	259 (95.6)
Clinically evaluable (CE) population n (%)[a]	199 (67.5)	198 (68.7)	223 (81.1)	213 (78.6)
Microbiologically evaluable (ME)[5] population [a]	115 (39)	113 (39.2)	164 (59.6)	148 (54.6)

[a] percentage calculated on the basis of the randomised population

At the time of inclusion, the demographic and medical characteristics of the patients were similar between the two treatment groups in both studies. The average age of the patients included was around 48 years (two-thirds men) and roughly 7% of patients were over 75. The most common infection in patients treated with TYGACIL was "cellulitis" (59%), followed by other infections, including major abscesses (27.5%). The number of diabetic patients with a foot infection (5%) and patients with a concomitant bacteraemia (3%) was limited. The number of patients with comorbidity factors such as diabetes (20%), peripheral vascular disease (7%), intravenous drug use (2%) and HIV infection (1%) was limited.

The mean duration of treatment with antibiotics was comparable between both groups in both studies (around 8 to 8.5 days).

[2] CE = c-mITT patients meeting the inclusion and exclusion criteria and who received sufficient appropriate treatment to determine whether they had been cured or the treatment had failed, where the failure or success was evaluated at the end of treatment.
[3] c-mITT = patients included in the ITT population who received at least one treatment dose and showed clinical evidence of cSSSI.
[4] mITT = patients who received at least one treatment dose.
[5] ME: CE patients with at least one isolated initial pathogenic agent sensitive to two treatments, along with a microbiological response that may be classified as eradication, persistence, super infection during the remote check-up at the end of treatment.

- Clinical response after treatment

	Study 3074A1-300-US / CA			Study 3074A1-305-WW		
	TYGACIL	**Vancomycin / aztreonam**	**95% CI ***	**TYGACIL**	**Vancomycin / aztreonam**	**95% CI ***
Clinically modified intention-to-treat (c-mITT) population						
	n = 277	**n = 260**		**n = 261**	**n = 259**	
Cure	209 (75.5)	200 (76.9)	**[-9.0** ; **6.1]**	220 (84.3)	225 (86.9)	**[-9.0 ; 3.8]**
Clinical failure	48 (17.3)	46 (17.7)		31 (11.9)	26 (10.0)	
Undetermined	20 (7.2)	14 (5.4)		10 (3.8)	8 (3.1)	
Clinically evaluable (CE) population						
	n = 199	**n = 198**		**n = 223**	**n = 213**	
Cure	165 (82.9)	163 (82.3)	**[-7.4 ; 8.6]**	200 (89.7)	201 (94.4)	**[-10.2 ; 0.8]**
Failure	34 (17.1)	35 (17.7)		23 (10.3)	12 (5.6)	

*Confidence interval of the difference (TYGACIL - vancomycin/aztreonam)

- Clinical success rate for different bacteria strains (ME population)

Pooled results (studies 300 - 305)	**TYGACIL**		**Vancomycin/ Aztreonam**	
Pathogen	n/N	%	n/N	%
Staphylococcus aureus (MSSA)	125/139	89.9	118/126	93.7
Staphylococcus aureus (MRSA)	24/31	77.4	25/33	75.8
Streptococcus pyogenes	31/33	93.9	24/27	88.9
Streptococcus anginosus [a]	16/20	-	9/10	-
Enterococcus faecalis[b]	13/17	-	24/29	-
Streptococcus agalactiae	8/8	-	11/13	-
Escherichia coli	27/32	84.4	26/30	86.7
Bacteroides fragilis	6/8	-	4/5	-

a: *Streptococcus anginosus: S. anginosus, S. anginosus ana, S.intermedius and S.constellatus.*
b: the *Enterococcus faecalis* pathogens were vancomycin-susceptible *Enterococcus sp*

- Microbiological responses (m-mITT[6] population)

In study 300, the microbiological eradication rate was 72.6% (135/186) in the TYGACIL group and 73.1% (125/171) in the vancomycin/aztreonam group.

S. aureus was isolated in 106 patients (43 MRSA) in the TYGACIL group and in 95 patients (39 MRSA) in the vancomycin/aztreonam group. The microbiological eradication rates were 73.6% in the TYGACIL group *versus* 78.9% in the vancomycin/aztreonam group (MRSA: 67.4% *versus* 82.1%).

In study 305, the microbiological eradication rate was 79.4% (166/209) in the TYGACIL group and 84.2% (171/203) in the vancomycin/aztreonam group.

S. aureus was isolated in 119 patients (13 MRSA) in the TYGACIL group and in 104 patients (13 MRSA) in the vancomycin/aztreonam group. The microbiological eradication rates were 80.7% in the TYGACIL group *versus* 85.6% in the vancomycin/aztreonam group.

3.1.2. Complicated intra-abdominal infections (cIAI)

The TYGACIL clinical development program included 2 pivotal non-inferiority studies (studies 301-WW and 306-WW) whose principal objective was to compare the efficacy and safety of tigecycline with those of imipenem/cilastatin in the treatment of complicated intra-abdominal

[6] m-mITT: c-mITT with at least one initial pathogenic agent.

infections during a course of intravenous treatments with a potential duration of up to 14 days (5 days minimum). TYGACIL would be considered non-inferior to the comparator treatment if the lower limit of the 95% confidence interval of the difference between the clinical success rates of TYGACIL and the comparator treatment was greater than -15%.

- Inclusion and exclusion criteria

To be included in the study, patients had to be hospitalised, be aged at least 18 years and require surgery and have a complicated intra-abdominal infection:

- intra-abdominal abscess
- intra-abdominal abscess (including liver and spleen) developed in a postoperative subject who received more than 48 hours but not more than 5 days of treatment with an antibiotic other than those studied.
- appendicitis complicated by a perforation or a periappendicular abscess
- perforated diverticulitis complicated by an abscess or faecal contamination
- complicated cholecystitis with evidence of perforation, empyema or gangrene
- perforation of a gastric or duodenal ulcer with symptoms evolving for more than 24 hours
- purulent peritonitis or peritonitis associated with faecal contamination
- perforated gastric or duodenal ulcer with symptoms evolving for more than 24 hours before the operation
- colic perforation or perforation of the small intestine with an abscess or faecal contamination lasting at least 12 hours before the operation.

Patients were not allowed to receive more than one dose of an antibiotic different to those evaluated after the initial sample had been taken.

These studies could not include patients who had received advance treatment with antibiotics for at least 5 days, an APACHE II score of more than 30, neutropenia or an intra-abdominal infection caused by at least one bacterial strain resistant to one of the study treatments (e.g. *P. aeruginosa* and *Proteus mirabilis*).

- Treatments

The eligible patients were randomised (stratified randomisation based on an APACHE II score $\leq$ 15 or > 15 but < 31) to receive:

- either TYGACIL administered by intravenous infusion (for 30 minutes) at the initial dose of 100 mg, followed by a dose of 50 mg every 12 hours;
- or imipenem/cilastatin administered by intravenous infusion at a dosage of 200 to 500 mg, according to body weight and creatinine clearance, every 6 hours.
  Note: The dose of imipenem/cilastatin administered was less than the recommended dose for severe infections due to sensitive bacteria (1 to 2 g, divided into 3 or 4 daily infusions).

- Primary endpoint:

The primary endpoint was the clinical response (cure or failure), assessed after the end of the treatment (for a minimum period of 12 days and a maximum period of 92 days) in the microbiologically evaluable (ME)[7] population or in the microbiologically-modified intention-to-treat (m-mITT)[8] population. A cure was defined as the complete resolution or improvement of the clinical signs and symptoms caused by the infection, such that no further antibiotic treatment was necessary.

[7] ME: CE patients with at least one isolated initial pathogenic agent susceptible to two treatments, along with a microbiological response that could be classified as eradication, persistence, super infection during the remote check-up at the end of treatment

[8] m-mITT: c-mITT with at least one initial pathogenic agent.

- Results of studies.

- Study population and treatment procedures

	Study 301		Study 306	
	TYGACIL	**Imipenem/ cilastatin**	**TYGACIL**	**Imipenem/ cilastatin**
Randomised (ITT population)	417	417	409	415
Randomised not treated	4	5	5	2
Modified intention-to-treat (mITT) population n (%)	413 (99.0)	412 (98.8)	404 (98.8)	413 (99.5)
Clinically modified intention-to-treat (c-mITT) population n (%)[a]	408 (97.8)	399 (95.7)	393 (96.1)	401 (96.6)
Clinically evaluable (CE) population n (%)[a]	341 (81.8)	351 (84.2)	344 (84.1)	346 (83.4)
Microbiologically modified intention-to-treat (m-mITT) population	309 (74.1)	312 (74.8)	322 (78.7)	319 (76.9)
Microbiologically evaluable (ME)[a] population	247 (59.2)	255 (61.1)	265 (64.8)	258 (62.2)

[a] percentage calculated on the basis of the mITT population

The demographic and medical characteristics of the patients were comparable between the two treatment groups in both studies. The average age of the patients was 49 years (61% men) in study 306 and 43 years (67.5% men) in study 301, and around 8% of patients were over 75. The most common infection in 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 for less than 24 hours (5%). Of these patients, 76% had associated diffuse peritonitis (identified during surgery). The mean APACHE II score was 6. The number of patients with a severe underlying pathology, such as immunodepressed patients, patients with an APACHE II score > 15 (4%) or with multiple intra-abdominal abscesses identified surgically (10%) was limited. The number of patients with a concomitant bacteraemia was also limited (6%).

The mean duration of treatment was 7.7 days in both studies.

- Clinical response after treatment

	Study 3074AI-301-WW			Study 3074AI-306-WW		
	TYGACIL	**Imipenem/ cilastatin**	**95% CI ***	**TYGACIL**	**Imipenem/ cilastatin**	**95% CI ***
Microbiologically evaluable (ME) population						
	n = 247	**n = 255**		**n = 265**	**n = 258**	
Cure n (%)	199 (80.6)	210 (82.4)	[-9.0 ; 5.4]	242 (91.3)	232 (89.9)	**[-4.0 ; 6.8]**
Apache II score						
≤ 15	195/238 (81.9)	208/247 (84.2)	[-9.4 ; 4.8]	237/260 (91.2)	232/258 (89.9)	[-4.2 ; 6.7]
> 15	4/9	2/8		5/5	0/0	
Failure n (%)	48 (19.4)	45 (17.6)		23 (8.7)	26 (10.1)	
Microbiologically modified intention-to-treat population						
	n = 309	**n = 312**		**n = 322**	**n = 319**	
Cure n (%)	227 (73.5)	244 (78.2)	[-11.8 ; 2.3]	279 (86.6)	270 (84.6)	**[-3.7 ; 7.7]**
Apache II score						
≤ 15	219/295 (74.2)	242/302 (80.1)	[-13.0 ; 1.2]	271/314 (86.3)	268/316 (84.8)	[-4.3 ; 7.3]
> 15	8/14	2/10		8/8	2/3	
Failure n (%)	63 (20.4)	55 (17.6)		34 (10.6)	36 (11.3)	

*Confidence interval of the TYGACIL - imipenem/cilastatin difference

- Clinical success rate for different bacteria strains (ME population)

Pooled results (studies 301 - 306)	**TYGACIL**		**Imipenem/cilastatin**	
Pathogen	n/N	%	n/N	%
Bacteroides fragilis	67/87	77.0	60/74	81.1
Citrobacter freundii	12/16	-	3/4	-
Clostridium perfringens	19/20	-	20/22	-
Enterobacter cloacae	14/16	-	16/17	-
Enterococcus faecalis (non-VRE)	25/33	75.8	35/47	74.5
Escherichia coli	281/329	85.4	298/343	86.9
Klebsiella oxytoca	19/20	-	18/20	-
Klebsiella pneumoniae	46/52	88.5	53/60	88.3
Peptostreptococcus micros	14/18	-	9/12	-
Staphylococcus aureus (non-MRSA)	26/29	-	22/24	-
Streptococcus anginosa	102/120	85.0	61/81	75.3

- Microbiological response (m-mITT population)
In study 301, the microbiological eradication rates were 73.5% in the tigecycline group *versus* 78.2% in the imipenem group.

In study 306, the microbiological eradication rates were 86.6% in the tigecycline group *versus* 84.6% in the imipenem group.

- Analysis of sub-groups
Sub-group analyses were carried out on the basis of clinical diagnosis. The highest success rates were observed in patients with complicated cholecystitis or a perforated gastric or duodenal ulcer. The response was less favorable in subjects with diverticulitis, abscess, bacteraemia, creatinine clearance < 70 ml/min and an APACHE II score > 10. An APACHE II score $\geq$ 10 was identified as the main predictor of the treatment's failure.

3.1.3. Support studies: infections caused by bacteria resistant to other antibiotics: study 307-WW, study 309-WW

Study 307 focused on MRSA infections treated with tigecycline *versus* vancomycin, as well as on vancomycin-resistant enterococci (VRE) infections treated with tigecycline *versus* linezolid. MRSA was the most frequently isolated pathogen. The clinical success rate in the microbiologically evaluable (ME) population was 81.4% (70/86) in the TYGACIL group *versus* 83.9% (26/31) in the vancomycin group. There were a total of six VRE infections. Clinical success: 3/3 in the TYGACIL group *versus* 2/3 in the linezolid group.

Study 309 (N=36 ME), which was non-comparative, concerned infections caused by resistant Gram-negative bacteria. The clinical success rate (ME population) was 72.2% (26/36). The clinical success rate based on isolated bacteria strains was as follows: *Acinetobacter baumannii* (14/17), *Enterobacter* sp (3/4), *Escherichia coli* (7/12) and *Klebsiella pneumoniae* (6/8).

These data are currently limited and cannot be used to draw sound conclusions on these matters of interest.

3.2. Adverse effects

A total of 1415 patients were treated with tigecycline in the Phase III clinical studies. Adverse events were reported in around 41% of patients treated with tigecycline. Treatment was discontinued due to the occurrence of adverse events in 5% of patients.

The most common adverse effects were nausea (20%) and vomiting (14%), which were the most common reason for discontinuing treatment. They were reversible, were of slight to moderate intensity and occurred after 1 to 2 days of treatment.

The incidence of severe adverse events was similar (13.3% *versus* 11.5%) in both treatment groups. There were three cases of pancreatitis in each group. It should be noted that these cases will be particularly well-monitored as part of the risk management plan, given the known association between pancreatitis and tetracyclines, which have a similar structure to that of the glycylcyclines.

Of the patients who received tigecycline, 2.5% (35/1415) died as opposed to 1.6% (22/1382) of the patients who received the comparator treatment. Most of the deaths occurred in the course of intra-abdominal infections. In all treatment groups the mortality rate was linked to advanced age, a higher APACHE II score and a diagnosed intestinal perforation. The proportion of deaths linked to sepsis or septic shock was 1.1% in the tigecycline group *versus* 0.4% in the comparator group. The Summary of Product Characteristics (SPC) for TYGACIL states that: "*the combination of tigecycline with other antibiotics should be considered when treating severely ill patients with complicated intra-abdominal infections (cIAI) secondary to clinically-apparent intestinal perforation, as well as when treating patients with incipient sepsis or in a state of septic shock*".

3.3. Conclusion

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.

- **Complicated skin and skin structure infections (cSSSI)**

The clinical success rates (cure and clinical improvement) in the clinically-modified intention-to-treat (c-mITT) population were around 76% (95% CI[9]: -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 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.

- **Complicated intra-abdominal infections (cIAI)**

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% CI[9]: -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.

[9] Confidence interval of the difference between TYGACIL and the comparator

Consequently, the data available does not make it possible to position this 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 amoxycillin 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 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 between pancreatitis and tetracyclines, which have a similar structure to that of the glycylcyclines.

4 CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual benefit

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

This medicinal product comes within the scope of curative treatment.

The efficacy/adverse effects ratio for this 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).

Expected 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 medicinal product is substantial.

4.2. Improvement in actual benefit

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.

4.3. 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.

4.4. Target population

The indications for TYGACIL are complicated skin and skin structure 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 multi-resistant bacteria infections sensitive to tigecycline and infections for which there is no alternative treatment available).

4.5. Transparency Committee recommendations

The Transparency Committee recommends the inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the Marketing Authorisation.